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A Carcinogenicity Bioassay of Isobutyl 2-Cyanoacrylate (IBC) in Fischer-344 Rats-- One-Year Interim Sacrifice Report

(Volume 1 of 2)

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A Carcinogenicity Bioassay of Isobutyl 2-Cyanoacrylate (IBC) in Fischer-344 Rats--One-Year Interim Sacrifice Report, Volume 1 of 2 (Toxicology Series 144)--Brown et al

In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

This material has been reviewed by Letterman Army Institute of Research and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. *(AR 360-5)*

for Richard A. Lockhart 30 March 85

Edwin S. Beatrice (date)
COL, MC
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This report covers the results from the first year of a two-year carcinogenicity bioassay of the tissue adhesive, isobutyl 2-cyanoacrylate (IBC). Four hundred seven 6-week old Fischer-344 rats were randomized into three groups (control, 10 ul IBC, and 100 ul IBC), each group containing both male and female animals. The IBC was administered by surgical implantation of liquid monomer directly onto the ventral capsule of the liver. The monomer was allowed to polymerize before two-layer closure of the abdominal incision.

Control animals received 100 ul of isotonic saline also by surgical implantation. Twenty-five animals were removed from the study during the first week after surgery because of underweight condition or post operative complications.

All animals were examined daily and weighed and palpated monthly. The animals presented with

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a variety of transitory clinical signs sporadically throughout the year in addition to the more permanent sequelae of the surgical procedure (xyphoid protuberance, corneal opacity). These signs were observed in all dose groups and could not be attributed to compound administration. The weight gain of the two IBC treatment groups was comparable to that recorded for the control group. During the first year, 17 animals died or were sacrificed; three were unscheduled deaths and 14 were unscheduled sacrifices.. At the end of the first year 60 animals, 10 males and 10 females from each of the three groups, were selected randomly for a scheduled interim sacrifice. Three hundred and five animals remained on study at the start of the second year.

A total of 77 animals (17 unscheduled and 60 scheduled) were evaluated at necropsy during the first year. Fourteen of 14 unscheduled animals and 39 of 40 scheduled animals that received the IBC had fibrotic adhesions between the liver and the omentum, peritoneal membrane, diaphragm, stomach, skin, and/or intestine. These lesions were characterized histologically as foreign body granulomatous reactions. Nine tumors were observed in three unscheduled (total four tumors) and five scheduled animals. The unscheduled animal tumors included an atriocaval epithelial mesothelioma (10 ul IBC male), a mononuclear cell leukemia of splenic origin (10 ul IBC female), and a pituitary adenoma and mononuclear cell leukemia (100 ul IBC female). The scheduled animal tumors included an endometrial stromal polyp (10 ul IBC female), testicular mesothelioma (10 ul IBC male), adrenal gland cortical adenoma (10 ul IBC male), and pituitary adenomas (control and 10 ul IBC males). These tumors were spontaneous lesions and were considered incidental to IBC treatment. All other gross or histopathological findings were also considered incidental to IBC treatment or were sequelae of the surgical procedure.

Results of this study indicate that IBC has no effect on survival, weight gain, or the clinical condition of rats during the first year following its implantation. The only gross or histopathological finding observed in the first year attributed to the IBC treatment was the presence of adhesions on and a granulomatous reaction of the liver and those adjacent organs that came in contact with the IBC. No tumors were observed during the first year that could be attributed to IBC treatment. Keywords: adhesions; neoplasms; surgery; (KT)

ABSTRACT

This report covers the results from the first year of a two-year carcinogenicity bioassay of the tissue adhesive, isobutyl 2-cyanoacrylate (IBC). Four hundred seven 6-week-old Fischer-344 rats were randomized into three groups (control, 10 ul IBC, and 100 ul IBC), each group containing both male and female animals. The IBC was administered by surgical implantation of the liquid monomer directly onto the ventral capsule of the liver. The monomer was allowed to polymerize before two-layer closure of the abdominal incision. Control animals received 100 ul of isotonic saline also by surgical implantation. Twenty-five animals were removed from the study during the first week after surgery because of underweight condition or postoperative complications.

All animals were examined daily and weighed and palpated monthly. The animals presented with a variety of transitory clinical signs sporadically throughout the year in addition to the more permanent sequelae of the surgical procedure (xyphoid protuberance, corneal opacity). These signs were observed in all dose groups and could not be attributed to compound administration. The weight gain of the two IBC treatment groups was comparable to that recorded for the control group. During the first year, 17 animals died or were sacrificed; three were unscheduled deaths and 14 were unscheduled sacrifices. At the end of the first year 60 animals, 10 males and 10 females from each of the three groups, were selected randomly for a scheduled interim sacrifice. Three hundred five animals remained on study at the start of the second year.

A total of 77 animals (17 unscheduled and 60 scheduled) were evaluated at necropsy during the first year. Fourteen of 14 unscheduled animals and 39 of 40 scheduled animals that received the IBC had fibrotic adhesions between the liver and the omentum, peritoneal membrane, diaphragm, stomach, skin, and/or intestine. These lesions were characterized histologically as foreign body granulomatous reactions. Nine tumors were observed in three unscheduled (total four tumors) and five scheduled animals. The unscheduled animal tumors included an atriocaval epithelial mesothelioma (10 ul IBC male), a mononuclear cell leukemia of splenic origin (10 ul IBC female), and a pituitary adenoma and mononuclear cell leukemia (100 ul IBC female). The scheduled animal tumors included an endometrial stromal polyp (10 ul IBC female), testicular mesothelioma (10 ul IBC male), adrenal gland cortical adenoma (10 ul IBC male), and pituitary adenomas (control and 10 ul IBC males). These tumors were spontaneous lesions and were considered incidental to IBC treatment. All other gross or histopathological findings were also considered incidental to IBC treatment or were sequelae of the surgical procedure.

Results of this study indicate that IBC has no effect on survival, weight gain, or the clinical condition of rats during the first year

following its implantation. The only gross or histopathological finding observed in the first year attributed to the IBC treatment was the presence of adhesions and a granulomatous reaction of the liver and those adjacent organs that came in contact with the IBC. No tumors were observed during the first year that could be attributed to IBC treatment.

Key Words: Chronic Toxicity, Isobutyl 2-Cyanoacrylate, IBC, Bucrylate®, Mammalian Toxicology, Tissue Adhesive, Carcinogenicity Bioassay, Rat

PREFACE

TYPE REPORT: Chronic Carcinogenicity Bioassay GLP Interim Study Report

TESTING FACILITY: US Army Medical Research and Development Command
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129-6800

SPONSOR: US Army Medical Research and Development Command
US Army Institute of Dental Research
Washington, DC 20307-5400
Project Officer: Eric S. Koppelman, LTC, DC

PROJECT/WORK UNIT/APC: Tissue Adhesive Project, 35162775A825, WU 015, APC TL11

GLP STUDY NUMBER: 83009

STUDY DIRECTOR: MAJ Don W. Korte Jr, PhD, MSC

PRINCIPAL INVESTIGATOR: MAJ Larry D. Brown, DVM, MPVM VC Diplomate, American College of Veterinary Preventive Medicine, American Board of Toxicology

CO-PRINCIPAL INVESTIGATORS: MAJ Catherine D. Smith, DVM VC
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TOXSYS® DATA MANAGER: Yvonne C. LeTellier, BS

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocol, retired SOPs, raw data, analytical, stability, and purity data of the test compound, tissues, microslides, and an aliquot of the test compound will be retained in the LAIR Archives.

TEST SUBSTANCE: Isobutyl 2-Cyanoacrylate (IBC), Bucrylate®

INCLUSIVE STUDY DATES: 11 January 1984 - 29 January 1985

OBJECTIVE: The objective of this study was to evaluate the carcinogenic/tumorgenic potential of isobutyl 2-

cyanoacrylate in male and female Fischer-344 rats subjected to lifetime (2 year) exposure of the implanted test material.

ACKNOWLEDGMENTS

Richard A. Spieler, RLAT (AALAS) and SGT Thomas W. Johnson assisted in the study. SSG James D. Justus and staff provided animal and facility management. Callie B. Crosby, Colleen S. Kamiyama, Dorothy L. Davis, and Dianna B. Johnson provided office management and secretarial assistance for this study and preparation of the report. LTC William G. Rodkey, DVM, Dipl, ACVS, COL William B. Carpenter, DDS, and LTC Eric S. Koppelman, DDS, performed the requisite surgery in support of this project. MAJ Michael J. Langford and MAJ Glen E. Marrs, Jr, veterinary pathologists, supported the early phases of this study. Histology technicians were Lucille Cote and Marge Henderson. COL John J. Kearney, LAIR/LAMC Staff Ophthalmologist, Ocular Hazards Division, was the eye consultant to this study. Eleanor M. Baker proofread the manuscript.

SIGNATURES OF PRINCIPAL SCIENTISTS AND MANAGERS INVOLVED IN THE STUDY

We, the undersigned, declare that the GLP Study 83009 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

10 FEB88
DON W. KORTE JR., PhD / DATE
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Study Director

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CONRAD R. WHEELER, PhD / DATE
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Chemist

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DEPARTMENT OF THE ARMY

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REPLY TO
ATTENTION OF:

SGRD-ULZ-QA 21 January 88

MEMORANDUM FOR RECORD

SUBJECT: Report of GLP Compliance for GLP Study 83009

1. I hereby certify that in relation to LAIR GLP Study 83009, the following inspections were made

23 August 1983	-	Protocol Review
17 January 1984	-	Weighing
23 January 1984	-	Weighing/Dosing
17 February 1984	-	Observation/Weighing/Palpitation
26 March 1984	-	Observation
17 May 1984	-	Observation
05 July 1984	-	Observation/Weighing
02 August 1984	-	Weighing/Palpitation

2. The report and raw data were reviewed on 2 February 1987 and 1 September 1987.

Carolyn M Lewis

CAROLYN M. LEWIS
Chief, Quality Assurance

TABLE OF CONTENTS

Volume 1

Table of Contents (continued)

A Carcinogenicity Bioassay of Isobutyl 2-Cyanoacrylate (IBC) in Fischer 344 Rats -- One-Year Interim Sacrifice Report--Brown et al

INTRODUCTION

Isobutyl 2-cyanoacrylate (IBC) is being evaluated by the U.S. Army Medical Department as a tissue adhesive for use in sutureless wound closure, oral and maxillofacial surgery, and in other surgical procedures. The use of this modality could provide a time-saving and sometimes life-saving dimension to the management of combat wounds. The U.S. Army Institute of Dental Research (USAIDR) has been assigned the mission of evaluating the therapeutic potential of IBC. As part of their mandate, USAIDR has tasked the Toxicology Branch, Letterman Army Institute of Research (LAIR), to evaluate IBC in a chronic carcinogenicity bioassay.

Objective of Study

The objective of this study was to evaluate the carcinogenic/tumorgenic potential of isobutyl 2-cyanoacrylate in male and female Fischer-344 rats subjected to lifetime (2-year) exposure of the implanted test material.

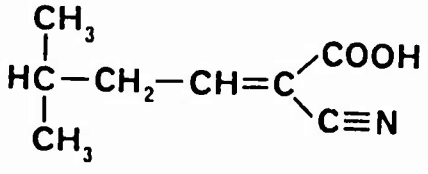
MATERIALS

Test Substance

Chemical name: Isobutyl 2-cyanoacrylate (IBC), Bucrylate®

Chemical Abstract Service (CAS) Registry No.: 1069-55-2

Molecular structure:



Molecular formula: $C_8H_{11}NO_2$

Other information on the test substance is presented in Appendix A.

Animal Data

Two hundred nine male and 210 female 4-week-old Fischer-344 (CDF) rats were received for this study on 11 Jan 84 from Charles River Breeding Laboratories, Inc, Wilmington, MA. They were identified individually with ear tags numbered 84D00001 to 84D00209 (inclusive) for the males and 84D00226 to 84D00435 (inclusive) for the females. Four males and 4 females were selected randomly for quality control necropsy evaluation at receipt. The animal weights on the day following receipt (12 Jan 84) ranged from 30 to 57 g. During quarantine three underweight females and one malocculded male were submitted to necropsy on 20 Jan 84. Additional animal data appear in Appendix B.

Husbandry

Animals used in this study were housed at LAIR in the Toxicology Suite (RS1419), a restricted access facility. Rats were caged individually in stainless steel wire-mesh cages in racks equipped with automatically flushing dumptanks. No bedding was used in any of the cages. The diet, fed ad libitum, consisted of Certified Purina Rodent Chow Diet 5002 (Ralston Purina Company, St. Louis, MO); tap water was provided by automatic water valves on a central line. Water was analyzed quarterly for impurities, bacteria, physical and chemical properties, organic residues, pesticides, and heavy metals. The animal temperature room and relative humidity were continuously recorded. The room was maintained at temperatures ranging from 21.2°C to 26.7°C and at a relative humidity range of 33 to 55%, except for short periods (spikes) during which cleaning of the room altered the relative humidity. On eleven occasions, when there were steam outages or when the fans were off, the relative humidity increased to 60-90% for 4- to 12- hour periods. The photoperiod of 12 hours of fluorescent light per day was electronically controlled. Air changes, cage size, and husbandry conformed to National Research Council (NRC) Institute of Laboratory Animal Resources (ILAR) standards (1). The LAIR animal facility is accredited by the American Association for Accredited Laboratory Animal Care (AAALAC).

METHODS

This study was performed in accordance with the protocol, applicable amendments and cited operating procedures including: LAIR Standard Operating Procedure OP-STX-81, "Chronic Bucrylate® Bioassay Procedures within Toxicology GLP Suite and Administrative Areas" (2); OP-STX-73, "Chronic Carcinogen Bioassay" (3); and FDA Nonclinical Laboratory Studies, Good Laboratory Practice Regulations (4).

Group Assignment/Acclimation

Study rats were randomized on 19 January 1984 into two experimental dose groups of 68 males and 68 females each and a saline control group of 68 males and 67 females. Allocation was accomplished by using the Beckman TOXSYS® (Beckman Instruments, Inc., Somerset, NJ) Animal Allocation Program. The animals were acclimated for 12 days before the day of dosing. During this period they were observed daily for signs of illness.

Dosage Levels

The following test doses were administered: high-dose group, 100 ul IBC/animal; low-dose group, 10 ul IBC/animal; and vehicle control group, 100 ul saline/animal.

Preparation of Compound

Bucrylate® IBC tissue adhesive (lot 929-252, Ethicon, Inc., Somerville, NJ) was received from the sponsor on 10 January 1984 as 750 0.5-ml-scored ampules in individual overwrap sterile bags. The IBC required no preparation prior to implantation. It was stored at LAIR in room LR1203A under darkness and at room temperature. Dosing of control animals was performed with commercial sterile isotonic (0.9%) saline (lot 56-329-FD-05, Expiration Date 1 Sep 86, Abbott Labs, Chicago, IL).

Chemical Analysis of IBC

Ethicon, Inc., provided data on infrared, chromatographic, and chemical analysis of the IBC (Appendix A). Lot 929-252 contained 99.9% (w/w) total monomer. Before dosing, the LAIR Analytical Chemistry Group verified the identity of the IBC by IR spectroscopy, confirmed the purity by gas chromatography, and demonstrated the stability of the IBC during the dosing period (Appendix A).

Test Procedures

The fixed volume of neat IBC or saline each animal received was based upon its assigned dosage group and was administered directly onto the ventral capsule of the liver. High-dose animals received 100 ul of IBC, low-dose animals received 10 ul of IBC, and control animals received 100 ul of saline. Rats were 6 weeks of age at dosing. Since the surgical survival rate for implantation of this compound was unknown, all animals, regardless of size, were subjected to the surgical procedure and dosed to insure that sufficient numbers would be available for inclusion in the chronic phase of the study. Body weights at dosing ranged from 29 to 123 g, with the mean male and female weights at 94.0 g and 73.8 g, respectively.

The test compound was implanted under sterile conditions in the LAIR Operating Room Suite on 23 and 24 Jan 84. The surgical laparotomy implantation procedure was performed under xylazine/ketamine anesthesia. Following anesthesia, surgical preparation and midline incision, the animal's liver was exposed by "tenting" the abdominal wall with either ophthalmic retractors or tissue forceps. The IBC was applied to the ventral capsule of the liver, usually the caudate lobe, by using either a sterile tip 100 ul or 10 ul fixed volume Eppendorf micropipette. The IBC was then allowed to polymerize for 2-3 minutes before closure. All pipettes used in the study were shown to be accurate within ± 2%. A two-layer closure with bioresorbable 4-0 Vicryl® (Ethicon, Inc.) and skin staples or skin clips was used. After the animals recovered to sternal recumbency, they were returned to the Toxicology Suite. A complete surgical report is provided in Appendix C.

Clinical Observations

On the day of dosing and during the following 2-week period, animals were checked intermittently throughout the day. During the first postoperative week, 25 animals were removed from the study due to underweight condition and/or complications. Three hundred eighty-two animals recovered satisfactorily and remained on study as of 1 Feb 84. After the animals were stabilized, observations for mortality and signs of toxicity or illness were reduced in frequency to twice daily. An observation was performed each morning according to the following procedure: (a) all animals were observed closely for signs of toxicity or illness without disturbing them in the cage; (b) once a week the animals (20% of them per work day) were removed from their cages and observed; (c) animals were observed after being returned to their cages. A second "walk-through, live/dead check" observation was performed every afternoon with only significant observations recorded. Monthly, a more detailed clinical examination was performed, body weights were obtained, and the abdomens of all animals were gently palpated. These data were recorded electronically on a Beckman TOXSYS® Data Collection Terminal. Daily observations/clinical signs were recorded on written records and significant changes entered into the TOXSYS® workstation. TOXSYS® software on the LAIR Data General Computers, Models MV8000 and C330, was used to analyze clinical signs and body weight data.

Pathological Examinations

Animals that were moribund at the time of clinical examination were euthanized by pentobarbital overdose, exsanguinated by axillary incision, and necropsied. During the first year three animals died unexpectedly (unscheduled), and 14 unscheduled sacrifices were required. Additionally, 60 animals (30 males and 30 females; the first 10 in numerical sequence from previously randomized groups) were submitted for a scheduled interim sacrifice at the end of the first year, 28-29 January 1985. Gross necropsy examinations were performed,

tissues were collected, and organs weighed for each animal in accordance with LAIR OP-STX-32, "General Pathology Procedures", OP-PSG-7, "Necropsy Procedure--Microscopic Examination of Small Laboratory Animals", and OP-PSG-12, "Histopathology--Trimming of Rodent Tissues." At necropsy, gross weights were recorded for the following 7 organs from each animal: brain, liver, spleen, kidneys, heart, adrenal glands, and testes or ovaries. Subsequently, organ/body weight ratios and organ/brain weight ratios were computed, and data were analyzed.

The pathologic evaluation consisted of gross and microscopic examination of major organs/tissues and all gross lesions from sacrificed animals and animals found dead. The following organs/tissues were examined microscopically: eyes and lens, skin, subcutaneous tissue, mammary gland, brain (4 levels, anterior cerebral, midcerebral, midbrain, cerebellum), middle ears, auditory canal, sebaceous gland, trachea, lungs, nasal region, sternum, heart, aorta, salivary glands (parotid, submaxillary, sublingual), harderian lacrimal and intraorbital lacrimal glands, exorbital lacrimal glands, liver (2-4 sections of various lobes), pancreas, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, kidneys, urinary bladder, accessory sex glands (male only--prostate, seminal vesicle, coagulating gland, epididymis), testes/ovaries, uterus (horns and body), skeletal muscle (2 sections, longitudinal and cross), sciatic nerve, tongue, pituitary, thyroid/parathyroid, adrenals, thymus, spleen (2 cross-sections), mesenteric lymph nodes, rib, femur (bone marrow), and vertebrae with spinal cord (3 sections, cervical, thoracic, and lumbar). These tissues were preserved in 10% buffered formalin, trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. Necropsy data were recorded and entered into a Xybion® (Xybion Medical Systems, Cedar Knoll, NJ), computerized data acquisition program designed for a DEC VAX 750 computer. Microscopic findings were entered into the computer directly as microslides were read. Since the Xybion® animal-numbering system was incompatible with the TOXSYS® numbering system used during the "in-life" phases of the study, the animals had to be renumbered by the Pathology Section as they were necropsied in order to enter them into the Xybion® Pathology Data System. These new numbers appear on all pathology reports along with the corresponding Toxicology number used during the "in-life" phase.

Statistical Analyses

Statistical analyses were performed on the study results. TOXSYS® System programs were used to determine the group mean animal body weights (EDS002)and the frequencies of clinical signs (EDS057-61). The Xybion® Pathology Data System was used to generate the pathology raw data listings, summary pathology reports, lesion frequency data, and statistical values for organ weights and organ weight ratios (mean, standard deviation, Bartlett's Test, ANOVA, and Dunnett's Test). The 5% ($p \leq 0.05$) level of significance was used for all tests.

Duration of Study

The "in-life" period of the study for the first year ran from 11 Jan 84, when the animals arrived at LAIR, until 29 Jan 85, when the interim sacrifice was completed. Appendix D is a complete listing of historical events.

Changes/Deviations from Protocol

Performance of this study was in accordance with the protocol and applicable amendments with the following exceptions: Daily room washdown/cleanup caused transient spikes in relative humidity, and on eleven occasions, steam outages or fan stoppage increased the animal room relative humidity up to 60-90% for 4- to 12-hour periods. These deviations from protocol did not significantly alter the outcome of the study.

Storage of Raw Data and Final Report

A copy of the final report, study protocol and amendments, raw data, relevant SOPs, analytical data for the test compound, and an aliquot of the test compound will be retained in the LAIR Archives.

RESULTS

Mortality

Three unscheduled deaths were recorded during the first year of the study. In addition, 14 animals were euthanized because they were moribund, had infections, had lost weight, or were in poor condition (Table 1).

Clinical Observations

The majority of animals gained and maintained weight and remained healthy throughout the first year of the study. Mean body weights of IBC-dosed and saline-treated control animals were comparable throughout the first year. Tables 2 (male) and 3 (female) present mean monthly body weights by group, and Figure 1 presents a graphic display of mean body weight versus time. Individual body weights can be found in the individual animal history reports (Volume 2, Appendix I).

TABLE 1

Listing of Unscheduled Deaths/Euthanized Animals
1 Feb 84 - 27 Jan 85

Toxicology Animal No.	Date	Reason	Sex	Dose Group
84D00318	3 Feb 84	Sacrificed--Corneal Ulcers	F	High IBC
150	17 Feb 84	Sacrificed--Moribund	M	High IBC
344	12 Mar 84	Sacrificed--Corneal Ulcers	F	Low IBC
253	30 Mar 84	Sacrificed--Conjunctivitis & Respiratory Infection	F	Control
065	3 Apr 84	Sacrificed--Subcutaneous Abscess	M	High IBC
421	4 Jun 84	Sacrificed--Poor Condition & Conjunctivitis	F	Low IBC
043	19 Jul 84	Sacrificed--Intra-abdominal Mass	M	High IBC
333	29 Aug 84	Sacrificed--Intra-abdominal Mass	F	High IBC
434	2 Oct 84	Sacrificed--Alopecia & Conjunctivitis	F	Low IBC
385	22 Oct 84	Sacrificed--Intra-abdominal Mass	F	High IBC
240	4 Dec 84	Sacrificed--Weight Loss	F	Control
277	11 Dec 84	Sacrificed--Infected Skin Lesion Base Tail	F	H C
242	13 Dec 84	Sacrificed--Erythematous Skin Around Head & Face	F	C
370	31 Dec 84	Sacrificed--Intra-abdominal Mass with Perianal Staining	F	High IBC
194	15 Jan 85	Died in Cage	M	Low IBC
377	15 Jan 85	Died in Cage	F	High IBC
236	19 Jan 85	Died in Cage	F	High IBC

TABLE 2

Mean Group Body Weights: Males -
Year One of Two-Year IBC Carcinogenicity Bioassay

Date	Observation Period	High Dose IBC (grams)	Low Dose IBC (grams)	Saline Controls (grams)
19 Jan 84	0	71.1 (68)*	70.8 (68)	70.7 (68)
16 Feb 84	1	184.6 (63)	189.8 (66)	190.4 (67)
15 Mar 84	2	240.5 (62)	245.5 (66)	244.6 (67)
12 Apr 84	3	275.0 (61)	279.0 (66)	279.4 (67)
10 May 84	4	300.4 (61)	304.4 (66)	303.8 (67)
7 Jun 84	5	318.0 (61)	322.2 (66)	321.9 (67)
5 Jul 84	6	331.4 (61)	333.2 (66)	334.3 (67)
2 Aug 84	7	345.8 (60)	346.9 (66)	347.5 (67)
30 Aug 84	8	360.7 (60)	362.8 (66)	360.1 (67)
27 Sep 84	9	368.1 (60)	370.6 (66)	370.9 (67)
25 Oct 84	10	380.9 (60)	381.3 (66)	383.8 (67)
22 Nov 84	11	389.2 (60)	389.5 (66)	390.9 (67)
20 Dec 84	12	390.2 (60)	391.7 (66)	393.6 (67)
17 Jan 85	13	393.9 (60)	396.7 (65)	399.6 (67)

19 January 1984 - Allocation Day
23 & 24 January 1984 - Dosing Day
28 January 1985 - Interim Sacrifice Day (Males)

*(n) number in group

TABLE 3

Mean Group Body Weights: Females -
Year One of Two-Year IBC Carcinogenicity Bioassay

Date	Observation Period	High Dose IBC (grams)	Low Dose IBC (grams)	Saline Controls (grams)
19 Jan 84	0	58.8 (68)*	58.5 (68)	58.8 (67)
17 Feb 84	1	126.1 (56)	125.7 (65)	125.3 (64)
16 Mar 84	2	156.6 (56)	154.8 (64)	155.3 (64)
13 Apr 84	3	173.1 (56)	171.8 (64)	171.7 (63)
11 May 84	4	184.2 (56)	181.2 (64)	181.1 (63)
8 Jun 84	5	191.6 (56)	188.8 (63)	188.9 (63)
6 Jul 84	6	194.5 (56)	191.4 (63)	191.1 (63)
3 Aug 84	7	203.1 (56)	199.3 (63)	199.7 (63)
31 Aug 84	8	205.0 (55)	201.6 (63)	200.6 (63)
28 Sep 84	9	211.5 (55)	208.5 (63)	207.6 (63)
26 Oct 84	10	219.0 (54)	213.0 (62)	211.4 (63)
23 Nov 84	11	222.8 (54)	216.8 (62)	215.0 (63)
21 Dec 84	12	226.5 (53)	219.7 (62)	218.7 (61)
18 Jan 85	13	233.5 (51)	225.1 (62)	222.4 (61)

19 January 1984 - Allocation Day
24 January 1984 - Dosing Day
29 January 1985 - Interim Sacrifice Day (Females)
*(n) number in group

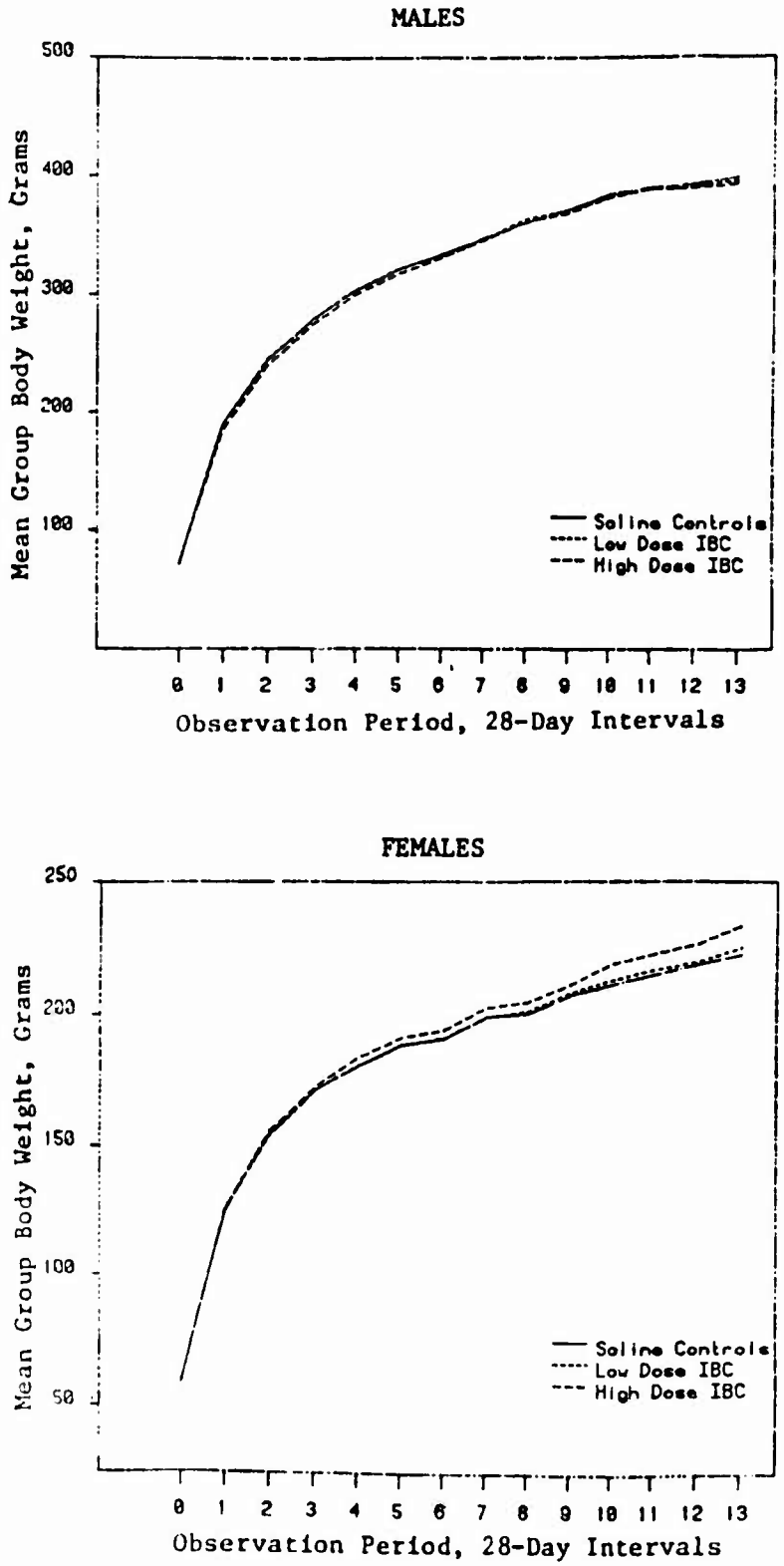


Figure 1. Growth Curves for F-344 Rats Administered Isobutyl 2-Cyanoacrylate by Intraperitoneal Implantation--Year One

Clinical signs were observed throughout the first year; however, the signs were generally routine and of minor consequence. Signs observed during the first year included corneal opacity, conjunctivitis, ocular abnormality, chromodacryorrhea, lacrimation, anterior body (face, mouth, head, chest and/or front limbs) staining, posterior body staining, ulcerated ear tag, dehydration, respiratory dysfunction, cutaneous scab, subcutaneous abscess, xyphoid protuberance, rough coat, alopecia, irritable behavior, nasal papilloma, hunched posture, malocclusion of incisors, accessory sex gland abnormality, postoperative complications, palpable intra-abdominal mass, self-mutilation, scaling tail, poor condition/emaciated, gastrointestinal dysfunction, hypotonia and death.

In general, clinical signs developed rapidly and were relatively mild and of short duration except for the eye conditions and the few iatrogenic postoperative abnormalities (xyphoid protuberance) which persisted through the end of the first year. Clinical sign summary reports are provided in Appendix E for unscheduled males, scheduled males, first-year survivor males, unscheduled females, scheduled females, and first-year survivor females.

The frequency of clinical signs was comparable among the two IBC dose groups and the saline control group. Postoperative complications were localized to the eyes and the abdominal incision. The ocular signs (conjunctivitis, corneal opacity, corneal edema, corneal ulceration, hyperemic iris vessels, neovascularization of cornea, chromodacryorrhea, hyphemia, dilated pupil, mydriasis and exophthalmos) observed in many of the animals were sequelae to drying (keratoconjunctivitis sicca) of the eyes during surgery (Appendix C). Corneal ulcers formed within 7-14 days. These lesions healed, leaving persistent corneal scars.

Some animals also had conjunctivitis and chromodacryorrhea which persisted for long periods. Streptococcus faecalis, a common normal flora bacterium, was cultured from these eyes. The consulting ophthalmologist reported that this low-grade ocular infection was limited to the globe and its accessory structures; therefore, no treatment was rendered. Other postsurgical complications included xyphoid cartilage protuberance/nodule (due to accidental incision of the xyphoid cartilage in some animals while attempting to expose the liver sufficiently), hernia of incision, peritonitis, and suture-line infection. Significant postoperative complications occurred in less than 5% of all animals.

Gross and Microscopic Pathology

Incidence summary reports for gross necropsy observations are found at Appendix F and incidence summary reports for microscopic observations are found at Appendix G for scheduled and unscheduled animals.

Unscheduled Animals

Seventeen animals, 4 males and 13 females, were found dead or were euthanized during the first year of the study. The unscheduled deaths included 3 animals which were found dead and 14 which were euthanized for various reasons (Table 4). Compound-related lesions were observed in all 14 IBC-treated animals in the unscheduled group (Table 5a).

TABLE 4

Summary of Unscheduled Deaths/Euthanasia
First Year (17 Animals)

	High Dose IBC	Low Dose IBC	Controls	Total
Number Found Dead	2	1	0	3
Atriocaval epithelial mesothelioma, heart	0	1	0	1
Friable ruptured spleen, pituitary tumor	1	0	0	1
No obvious cause of death	1	0	0	1
Number Euthanized	8	3	3	14
With palpable intra-abdominal mass	4	0	0	4
In poor condition, emaciated or moribund	1	1	1	3
For infection control purposes	3	2	2	7

TABLE 5a

Gross and Microscopic Lesions - Unscheduled Deaths
(Compound-Related Lesions)

Reaction	Male			Female		
	High Dose IBC	Low Dose IBC	Control	High Dose IBC	Low Dose IBC	Control
(Number of Animals/Group)	3	1	0	7	3	3
Liver						
Gross: adhesions	3	1	0	7	3	0
Microscopic: capsular foreign granulomatous reaction	3	1	0	7	3	0
Skin						
Compound/inflammatory reaction	0	0	0	1	0	0
Duodenum						
Compound/inflammatory reaction	0	0	0	1	0	0
Ileum						
Compound/inflammatory reaction	1	0	0	1	0	0
Cecum						
Compound/inflammatory reaction	0	0	0	1	0	0
Stomach						
Compound/inflammatory reaction	0	0	0	1	0	0

See Volume 2 - Appendix J for glossary.

Macroscopically, these lesions presented as gross fibrous adhesions between the liver and adjacent tissues. These adhesions were sufficiently severe that the function and patency of the involved viscera were probably affected. Microscopically, a foreign-body granulomatous reaction of the liver capsule and parenchyma was evident in these animals. Similar compound-related lesions were noted occasionally in the abdominal skin, duodenum, ileum, cecum, and/or stomach.

Three animals in the unscheduled death group had tumors (Table 5b). One low-dose male (84D00194) had an atriocaval epithelial mesothelioma of the heart. One high-dose female (84D00236) had a pituitary adenoma. This high-dose female (84D00236) and one control female (84D00240) had large granular, lymphocytic, Fischer-344 leukemia (mononuclear cell leukemia) of splenic origin.

Incidental microscopic lesions were observed primarily in the liver, kidney, and eyes (Table 5c). Bile duct hyperplasia was present in 1 of 3 control and 6 of 14 IBC-treated animals. Hepatitis was noted in 2 of 10 IBC-treated females. Progressive renal disease was present in 1 of 3 control and 4 of 14 IBC-treated animals. Ocular lesions were observed primarily in the female animals. Other incidental lesions were noted only sporadically among the control and treatment groups.

TABLE 5b

Gross and Microscopic Lesions - Unscheduled Deaths
(Neoplasia/Tumor)

Reaction	Male			Female		
	High Dose	Low Dose	Control	High Dose	Low Dose	Control
(Number of Animals/Group)	3	1	0	7	3	3
Heart						
Atriocaval epithelial mesothelioma	0	1	0	0	0	0
Spleen						
Mononuclear cell leukemia	0	0	0	1	0	1
Pituitary						
Adenoma	0	0	0	1	0	0

TABLE 5c

Gross and Microscopic Lesions - Unscheduled Deaths
(Incidental Lesions)

Reaction	Male			Female		
	High Dose	Low Dose	Control	High Dose	Low Dose	Control
(Number of Animals/Group)	3	1	0	7	3	3
Liver						
Bile duct hyperplasia	1	1	0	4	0	1
Hepatitis	0	0	0	1	1	0
Necrosis	1	0	0	0	0	0
Kidney						
Progressive renal disease	1	0	0	2	1	1
Spleen						
Gross: Enlarged	0	0	0	1	0	1
Microscopic: Infarction	0	0	0	0	0	1
Eyes - Gross						
Corneal opacity	0	0	0	1	2	0
Ocular discharge	0	0	0	1	1	0
Conjunctivitis	0	0	0	0	0	1
Eyes - Microscopic						
Corneal mineralization	0	0	0	1	2	0
Corneal vascularization	0	1	0	1	1	0
Chronic keratitis	0	0	0	2	2	0
Iridocyclitis	0	0	0	1	0	0
Pancreas						
Peritonitis	1	0	0	1	0	0
Acinar (exocrine) atrophy	0	0	0	0	1	0
Lung						
Pulmonary edema	0	1	0	0	0	0
Vascular congestion	0	1	0	0	0	0
Skin						
Nonsuppurative dermatitis	0	0	0	0	1	0
Mammary gland						
Hyperplasia	0	1	0	0	0	0
Bone femur						
Myeloid hyperplasia	1	0	0	0	0	0

Scheduled Animals

Compound-related lesions were observed in 39 of 40 IBC-treated animals from the interim (scheduled) sacrifice group (Table 6a). These lesions were similar to those observed in the unscheduled animals as they presented macroscopically as gross fibrous adhesions between the liver and the diaphragm, abdominal wall, and/or visceral organs, and microscopically as a foreign-body granulomatous reaction of the liver capsule and parenchyma. Microscopic lesions in the skin, jejunum, cecum, and/or stomach were similar to those observed in the liver. Two of 10 male control group animals had gross adhesions, but there was no microscopic evidence of inflammation.

Tumors were detected in 5 rats in the scheduled group (Table 6b). One low-dose female (84D00244) had an endometrial stromal polyp; one low-dose male (84D00003) had a testicular mesothelioma; one low-dose male (84D00004) had an adrenal gland cortical adenoma; and one low-dose male (84D00029) and one control male (84D00008) had pituitary adenomas.

Incidental lesions, as with the unscheduled animals, were observed primarily in the liver (Table 6c). Bile duct hyperplasia was present in virtually all animals. Hepatitis was noted with equal distribution in all groups. Other incidental or background liver changes observed were basophilic focus, hepatocyte vacuolation, telangiectasis, capsular fibrosis, and clear focus. Equal numbers of animals in the control and treated groups were diagnosed with progressive renal disease and cardiomyopathy. There was a higher incidence (almost twice) of these lesions in males versus females. Ocular lesions were also reported in all groups. These diagnoses were based primarily on findings from the gross examination, although microscopic changes of corneal mineralization and vascularization were also present. Other incidental lesions were noted sporadically at necropsy and were either related to the surgery (xyphoid protuberance) or were considered incidental findings (pituitary cyst, uterine polyp, enlarged spleen).

TABLE 6a

Gross and Microscopic Lesions - Interim Sacrifice
(Compound-Related Lesions)

Reaction	Male			Female		
	High Dose	Low Dose	Control	High Dose	Low Dose	Control
(Number of Animals/Group)	10	10	10	10	10	10
Liver - Gross						
Adhesions	10	9	2	9	7	0
Liver - Microscopic						
Capsular foreign body granulomatous reaction	10	10	0	10	9	0
Necrosis	5	1	0	0	0	0
Skin						
Compound present/associated inflammatory fibrosis	1	0	0	0	0	0
Jejunum						
Compound/inflammatory reaction	0	0	0	1	0	0
Cecum						
Compound/inflammatory reaction	1	0	0	0	0	0
Stomach						
Compound/inflammatory reaction	0	0	0	2	0	0

See Volume 2, Part 2 - Appendix J for glossary.

TABLE 6b

Gross and Microscopic Lesions - Interim Sacrifice
(Neoplasia/Tumors)

Reaction	Male			Female		
	High Dose	Low Dose	Control	High Dose	Low Dose	Control
(Number of Animals/Group)	10	10	10	10	10	10
Uterus						
Endometrial stromal polyp	N/A	N/A	N/A	0	1	0
Testes						
Mesothelioma	0	1	0	N/A	N/A	N/A
Adrenal Gland						
Cortical adenoma	0	1	0	0	0	0
Pituitary						
Adenoma	0	1	1	0	0	0

TABLE 6c

Gross and Microscopic Lesions - Interim Sacrifice
(Incidental Lesions)

Reaction	Male			Female		
	High Dose	Low Dose	Control	High Dose	Low Dose	Control
(Number of Animals/Group)	10	10	10	10	10	10
Liver						
Bile duct epithelial hyperplasia	10	10	9	9	8	7
Hepatitis	3	2	3	6	3	3
Basophilic focus	0	2	1	3	1	2
Hepatocytic vacuolation	1	0	1	2	1	0
Telangiectasis	1	0	0	0	0	0
Capsular fibrosis no compound present	0	0	2	0	0	1
Focus, clear	0	0	0	0	0	1
Kidney						
Progressive renal disease	9	10	10	5	2	3
Heart						
Cardiomyopathy	6	3	3	2	2	2
Spleen						
Splenic corpuscle hyperplasia	0	0	0	1	0	0
Pituitary						
Cysts	0	0	0	0	2	3
Eyes - Gross						
Corneal opacity, irregularity	1	4	4	7	9	3
Eyes - Microscopic						
Metaplastic scleral bone	0	0	0	1	0	0
Corneal mineralization	0	0	1	3	2	2
Progressive retinal atrophy	0	2	0	0	0	0
Scleral mineralization	0	1	0	0	0	0
Corneal pigmentation	0	0	0	0	1	0
Corneal vascularization	0	0	0	0	0	1
Chronic keratitis	0	0	0	0	0	2

Tumor Incidence

Tumor incidences among the control and treated groups were comparable for both the unscheduled and scheduled animal groups. Table 7 presents tumor incidence data, by sex and dose group, for unscheduled and scheduled group animals, and for the total of unscheduled and scheduled group animals.

Organ Weight Data

Statistical data for absolute organ weights, organ/body weight percent ratios, and organ/brain weight percent ratios are presented in Tables 8a-d. Only the liver weights from the scheduled female high-dose group animals were different from control values. In this group, gross liver weights were significantly heavier, and liver/body weight and liver/brain weight percent ratios were significantly greater than those of the controls.

Quality Control Animals

Evaluation of the eight quality control animals upon their arrival revealed no lesions.

The individual animal pathology reports are provided in Volume 2, Part 2, Appendix K.

TABLE 7

Tumor Incidence - Unscheduled & Scheduled First Year

Condition	High-Dose IBC Male	High-Dose IBC Female	Low-Dose IBC Male	Low-Dose IBC Female	Control Male	Control Female	Total
Unscheduled							
Atriocaval epithelial mesothelioma, heart	0	0	1	0	0	0	1
Mononuclear cell leukemia of splenic origin	0	1	0	0	0	1	2
Pituitary adenoma	0	1	0	0	0	0	1
Neoplasia cases*/number of animals in group	0/3	2/7†	1/1	0/3	0/0	1/3	4/17 (23.5%)
Scheduled							
Endometrial stromal polyp	N/A	0	N/A	1	N/A	0	1
Mesothelioma, testes	0	N/A	1	N/A	0	N/A	1
Adrenal gland cortical adenoma	0	0	1	0	0	0	1
Pituitary adenoma	0	0	1	0	1	0	2
Neoplasia cases/number of animals in group	0/10	0/10	3/10	1/10	1/10	0/10	5/60 (8.3%)
Unscheduled and Scheduled Combined							
Total neoplasia cases/ number of animals/group	0/13	2/17	4/11	1/13	1/10	1/13	9/77 (11.7%)

* A case is equivalent to one animal with one tumor (one or more lesions) of a given classification. Animal with two different types of tumors is considered two cases.

† Both tumors in same animal (#84D00236).

TABLE 8a

Group Comparison Statistics for Absolute Organ Weight*, Percent Organ-to-Body Weight Ratio, and Percent Organ-to-Brain Weight Ratio -- Unscheduled Males

Organ	High Dose IBC	Low Dose IBC	Control
(Number/Group)	3	1	0
Group Mean Body Wt	230.7	373.0	N/A
Standard Deviation	72.6	N/A	N/A
Liver Absolute Wt*	± 2.4	13.5	N/A
Liver/Body Wt % Rati	± 0.1	3.6	N/A
Liver/Brain Wt % Rati	± 102.3	664.6	N/A
Kidneys Absolute Wt	1.7 ± 0.4	2.8	N/A
Kidneys/Body Wt % Ratio	0.7 ± 0.1	0.8	N/A
Kidneys/Brain Wt % Ratio	92.6 ± 17.5	139.3	N/A
Adrenal Glands Absolute Wt	0.064 ± 0.004	0.07	N/A
Adrenal/Body Wt % Ratio	0.03 ± 0.01	0.02	N/A
Adrenal/Brain Wt % Ratio	3.6 ± 0.1	3.4	N/A
Testes Absolute Wt	2.6 ± 0.4	2.8	N/A
Testes/Body Wt % Ratio	1.2 ± 0.2	0.8	N/A
Testes/Brain Wt % Ratio	145.9 ± 14.4	140.1	N/A
Heart Absolute Wt	0.6 ± 0.1	5.5	N/A
Heart/Body Wt % Ratio	0.29 ± 0.04	1.5	N/A
Heart/Brain Wt % Ratio	36.6 ± 4.4	272.0	N/A
Spleen Absolute Wt	0.67 ± 0.04	1.0	N/A
Spleen/Body Wt % Ratio	0.3 ± 0.1	0.3	N/A
Spleen/Brain Wt % Ratio	36.7 ± 20.9	51.8	N/A
Brain Absolute Wt	1.8 ± 0.2	2.0	N/A
Brain/Body Wt % Ratio	0.8 ± 0.2	0.5	N/A
Brain/Brain Wt % Ratio	100.0 ± 0.0	100.0	N/A

*Organ Weight in grams ± Standard Deviation

TABLE 8b

Group Comparison Statistics for Absolute Organ Weight*, Percent Organ-to-Body Weight Ratio, and Percent Organ-to-Brain Weight Ratio -- Unscheduled Females

Organ	High-Dose IBC	Low-Dose IBC	Control
(Number/Group)	7	3	3
Group Mean Body Wt	190.6	180.7	176.0
Standard Deviation	± 46.9	± 16.8	± 20.7
Liver Absolute Wt*	8.0 ± 3.2	6.6 ± 0.9	8.3 ± 3.8
Liver/Body Wt % Ratio	4.2 ± 1.1	3.6 ± 0.4	4.7 ± 2.3
Liver/Brain Wt % Ratio	467.4 ± 183.6	388.9 ± 54.3	353.7 ± 45.6
Kidneys Absolute Wt	1.6 ± 0.3	1.3 ± 0.1	2.3 ± 1.2
Kidneys/Body Wt % Ratio	0.8 ± 0.2	0.74 ± 0.04	1.3 ± 0.7
Kidneys/Brain Wt % Ratio	92.2 ± 22.0	78.7 ± 5.8	96.3 ± 22.0
Adrenal Glands Absolute Wt	0.06 ± 0.02	0.06 ± 0.02	0.6 ± 1.0
Adrenal/Body Wt % Ratio	0.033 ± 0.007	0.03 ± 0.01	0.4 ± 0.6
Adrenal/Brain Wt % Ratio	3.7 ± 1.3	3.2 ± 0.7	19.2 ± 28.0
Heart Absolute Wt	0.7 ± 0.2	0.6 ± 0.7	1.4 ± 1.3
Heart/Body Wt % Ratio	0.36 ± 0.06	0.35 ± 0.02	0.8 ± 0.8
Heart/Brain Wt % Ratio	40.0 ± 12.1	37.1 ± 0.3	50.9 ± 25.1
Spleen Absolute Wt	1.4 ± 2.5	0.42 ± 0.04	3.2 ± 4.8
Spleen/Body Wt % Ratio	0.6 ± 1.0	0.23 ± 0.02	1.9 ± 2.8
Spleen/Brain Wt % Ratio	81.8 ± 138.0	24.7 ± 2.5	98.5 ± 128.4
Ovaries Absolute Wt	0.11 ± 0.05	0.08 ± 0.02	0.7 ± 1.0
Ovaries/Body Wt % Ratio	0.06 ± 0.02	0.05 ± 0.01	0.4 ± 0.6
Ovaries/Brain Wt % Ratio	6.7 ± 3.2	4.9 ± 1.5	20.2 ± 26.6
Brain Absolute Wt	1.7 ± 0.2	1.7 ± 0.1	2.3 ± 1.0
Brain/Body Wt % Ratio	1.0 ± 0.3	0.93 ± 0.04	1.4 ± 0.6
Brain/Brain Wt % Ratio	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0

*Organ Weight in grams ± Standard Deviation

TABLE 8c

Group Comparison Statistics for Absolute Organ Weight*, Percent Organ-to-Body Weight Ratio, and Percent Organ-to-Brain Weight Ratio -- Scheduled Males

Organ	High-Dose IBC	Low-Dose IBC	Control
(Number/Group)	10	10	10
Group Mean Body Wt	386.3	388.6	388.3
Standard Deviation	± 18.3	± 21.4	± 28.4
Liver Absolute Wt*	11.7 ± 1.5	10.5 ± 1.0	10.7 ± 1.0
Liver/Body Wt % Ratio	3.0 ± 0.4	2.7 ± 0.2	2.8 ± 0.2
Liver/Brain Wt % Ratio	606.2 ± 86.1	538.5 ± 45.9	557.8 ± 50.7
Kidneys Absolute Wt	2.4 ± 0.2	2.5 ± 0.2	2.5 ± 0.2
Kidneys/Body Wt % Ratio	0.63 ± .03	0.63 ± .03	0.65 ± 0.03
Kidneys/Brain Wt % Ratio	126.8 ± 10.4	126.7 ± 8.1	131.1 ± 10.5
Adrenal Glands Absolute Wt	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01
Adrenal/Body Wt % Ratio	0.020 ± 0.003	0.020 ± 0.004	0.020 ± 0.004
Adrenal/Brain Wt % Ratio	3.5 ± 0.7	3.8 ± 0.7	3.5 ± 0.8
Testes Absolute Wt	3.2 ± 0.3	3.1 ± 0.1	3.1 ± 0.4
Testes/Body Wt % Ratio	0.83 ± 0.09	0.80 ± 0.04	0.79 ± 0.08
Testes/Brain Wt % Ratio	166.3 ± 14.5	160.3 ± 6.7	160.0 ± 15.4
Heart Absolute Wt	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.1
Heart/Body Wt % Ratio	0.31 ± 0.05	0.30 ± 0.05	0.29 ± 0.04
Heart/Brain Wt % Ratio	62.4 ± 10.2	60.3 ± 10.8	59.9 ± 6.6
Spleen Absolute Wt	0.69 ± 0.04	0.68 ± 0.05	0.69 ± 0.04
Spleen/Body Wt % Ratio	0.178 ± 0.009	0.174 ± 0.008	0.18 ± 0.01
Spleen/Brain Wt % Ratio	35.7 ± 3.1	34.76 ± 2.2	35.8 ± 2.5
Brain Absolute Wt	1.9 ± 0.1	1.9 ± 0.1	1.9 ± 0.1
Brain/Body Wt % Ratio	0.50 ± 0.03	0.50 ± 0.02	0.50 ± 0.04
Brain/Brain Wt % Ratio	100.00 ± 0.03	100.0 ± 0.0	100.0 ± 0.0

*Organ Weight in grams ± Standard Deviation

TABLE 8d

Group Comparison Statistics for Absolute Organ Weight*, Percent Organ-to-Body Weight Ratio, and Percent Organ-to-Brain Weight Ratio -- Scheduled Females

Organ	High-Dose IBC	Low-Dose IBC	Control
(Number/Group)	10	10	10
Group Mean Body Wt	222.6	211.9	209.2
Standard Deviation	± 13.4	± 14.2	± 14.0
Liver Absolute Wt	7.4 ± 1.4†	6.1 ± 0.5	5.7 ± 0.4
Liver/Body Wt % Ratio	3.3 ± 0.5†	2.9 ± 0.2	2.7 ± 0.2
Liver/Brain Wt % Ratio	432.8 ± 90.5†	345.0 ± 31.2	324.8 ± 30.5
Kidneys Absolute Wt	1.6 ± 0.1	1.6 ± 0.1	1.5 ± 0.1
Kidneys/Body Wt % Ratio	0.7 ± 0.03	0.74 ± 0.05	0.73 ± 0.04
Kidneys/Brain Wt % Ratio	93.4 ± 8.4	88.2 ± 7.6	86.3 ± 4.7
Adrenal Glands Absolute Wt	0.08 ± 0.01	0.07 ± 0.01	0.08 ± 0.02
Adrenal/Body Wt % Ratio	0.036 ± 0.006	0.034 ± 0.006	0.038 ± 0.009
Adrenal/Brain Wt % Ratio	4.6 ± 0.8	4.1 ± 0.7	4.6 ± 1.4
Heart Absolute Wt	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.1
Heart/Body Wt % Ratio	0.34 ± 0.03	0.36 ± 0.04	0.36 ± 0.03
Heart/Brain Wt % Ratio	44.5 ± 4.7	43.0 ± 6.2	42.2 ± 4.2
Spleen Absolute Wt	0.6 ± 0.2	0.46 ± 0.03	0.46 ± 0.01
Spleen/Body Wt % Ratio	0.25 ± 0.09	0.22 ± 0.01	0.22 ± 0.03
Spleen/Brain Wt % Ratio	32.5 ± 14.1	25.8 ± 1.8	26.1 ± 2.7
Ovaries Absolute Wt	0.10 ± 0.01	0.15 ± 0.13	0.12 ± 0.04
Ovaries/Body Wt % Ratio	0.044 ± 0.007	0.07 ± 0.06	0.06 ± 0.02
Ovaries/Brain Wt % Ratio	5.7 ± 0.7	8.54 ± 7.41	6.7 ± 2.2
Brain Absolute Wt	1.7 ± 0.1	1.8 ± 0.1	1.76 ± 0.4
Brain/Body Wt % Ratio	0.78 ± 0.07	0.84 ± 0.06	0.84 ± 0.06
Brain/Brain Wt % Ratio	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.3

*Organ Weight in grams ± Standard Deviation

†Significantly greater than control - Dunnett's Test of Significance ($p \leq 0.05$)

DISCUSSION

This report records the findings from the first year of a two-year carcinogenicity bioassay of IBC. This includes complete clinical histories and gross and microscopic pathological data on all unscheduled and scheduled (interim sacrifice) animals as well as complete clinical histories on all animals surviving the first year of the study.

Four hundred seven 6-week-old Fischer-344 rats were randomized into 3 dose groups. These rats received either saline, 10 ul IBC, or 100 ul IBC administered directly onto the ventral capsule of the liver via a surgical implantation technique.

The clinical history findings indicated that male and female animals treated with IBC gained weight at the same rate as the control animals. These findings also indicated that, as a whole, the animals in this study remained relatively healthy throughout the first year. Clinical signs observed during this period generally developed rapidly and were of short duration and of little clinical significance. Ocular conditions, which were secondary to desiccation of the eyes during surgery, were limited to the globe and accessory structures and had no significant impact on the animal's health. Other postsurgical complications, e.g., xyphoid protuberance, were also insignificant to the outcome of the study.

Seventeen animals died or were euthanized at various times during the first year. These animals were thus considered unscheduled animals. IBC-treated animals in the unscheduled group had compound-related gross fibrous adhesions between the liver and the diaphragm, abdominal wall, and/or visceral organs. A similar lesion was observed in IBC-treated animals euthanized at the interim sacrifice (scheduled animals). Microscopically, these lesions were characterized as a foreign-body granulomatous reaction involving the liver capsule and parenchyma. These changes were reflected in an increase in absolute and relative liver weights which were significant in the scheduled high-dose female groups. The scheduled high-dose male groups' liver weight parameters were of borderline significance. The most likely reason for increased liver weights in rats receiving high doses of the test material is the presence of fibrous adhesions and inflammation at the site of application. This could be attributed to the relatively large fixed volume of IBC (100 ul) administered to both male and female high-dose animals.

Tumors were observed in four unscheduled and five scheduled animals. One unscheduled animal had an unusual tumor involving the base of the heart. Microscopically, this tumor was characteristic of an adenocarcinoma, and it resembled, in all respects, lesions observed in the NZR/Gd strain of rats from New Zealand (5). The term atriocaval epithelial mesothelioma has been proposed for this lesion. While the incidence of this tumor in NZR/Gd rats is high (20% of

animals greater than one year of age), it is exceedingly rare in F-344 and other strains of rats. There has been no published report of this tumor occurring in other strains of rats. Its occurrence in one rat in this study is probably unrelated to administration of the test compound.

Two unscheduled animals had large granular lymphocyte leukemia (mononuclear cell leukemia), which is commonly observed in 10-35% of Fischer-344 rats over 18 months of age (6). Thirty to fifty percent of F-344 rats allowed to live a normal life span die from this disease (7). One unscheduled and two scheduled animals had pituitary adenomas. Endocrine tumors such as these or the adrenal cortical adenoma are common in aging F-344 rats (8,9) and consequently were not considered due to the test compound. Other tumors observed in the scheduled animals included an endometrial stromal polyp in a female. Expected incidence of this tumor is 12-18% (8,9). One male had a microscopically detected mesothelioma of the testes. Mesotheliomas are the most common neoplasm of the pleural/peritoneal cavity of F-344 rats. They occur primarily in males and most frequently involve the serous membrane of the abdominal cavity, commonly arising on the vaginal tunic of the scrotal sac. Incidence in aged F-344 rats is 1.3-4.0% (8,9).

Other incidental microscopic lesions were observed most frequently in the liver of both unscheduled and scheduled animals. Bile duct hyperplasia was observed in the majority of animals in both control and treated groups. It is a common lesion in aging F-344 rats, occurring in 24.5% of males and 12.5% of females which have lived for 2 years (8). Early trace evidence of rat chronic renal disease was described as progressive renal disease (see Appendix J). Progressive renal disease (PRD) was diagnosed with equal frequency in control and treated scheduled animals and was interpreted as early evidence of this chronic disease syndrome. Males had a higher incidence of PRD than did females. Lesions included in this syndrome were progressive degeneration of tubules, glomeruli, interstitium, and blood vessels. The reported incidence of progressive renal disease in 2-year-old F-344 rats is 66% in males and 38% in females (8). Another significant incidental lesion in the scheduled animals was cardiomyopathy which included myocardial degeneration, fibrosis, and chronic interstitial myocarditis. The repeated incidence of this lesion in 2-year-old F-344 rats is 33% in males and 17% in females (8). Inspection of the incidence data for progressive renal disease and cardiomyopathy in the scheduled animals reveals a similar sex-related distribution (twice the incidence in males as females). The reduced incidence rates observed for the unscheduled animals are attributable to the fact that these animals were often considerably younger at necropsy.

The ocular lesions were considered incidental to compound administration as they were distributed equally in both control and treated animals. The ocular changes were first observed within 14 days of the surgical procedure and considered to be the result of

prolonged anesthesia without corneal lubrication, causing keratoconjunctivitis sicca with subsequent corneal lesions. Ketamine hydrochloride anesthesia is one of two probable causative factors as it inhibits the blink reflex (10), allowing the eyes to dry out. Females were more severely affected because larger doses of anesthetic were required to achieve surgical anesthesia, resulting in prolonged postoperative recovery. The natural protrusion of the rats' ocular globe was also a probable causative factor for the dry eye condition. Other lesions observed at necropsy were incidental as they were related either to the surgery (xyphoid protuberance) or could not be attributed to the test compound (pituitary cysts, uterine polyp and enlarged spleen).

CONCLUSION

During the first year of this two-year carcinogenicity bioassay of IBC, there were no treatment-related changes in survival, weight gain, or clinical condition of the rats. The only compound-related lesions observed in animals during the first year were adhesions and/or local granulomatous reactions of the liver or other abdominal organs. No liver or other soft tissue tumors or neoplasia were observed during the first year that could be attributed to the chronic implantation of IBC in the Fischer-344 rat.

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Page

Volume 1

Volume 2 - Part 1

Volume 2 - Part 2

Appendices

CHEMICAL DATA

Chemical name: Isobutyl 2-cyanoacrylate

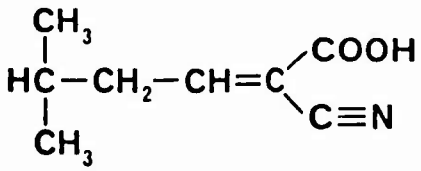
Other Listed Names: Bucrylate®, 2-cyano-2-propenoic acid 2-methyl-propyl ester, 2-cyanoacrylic acid isobutyl ester, bucrilate, IBC, IBCA*

Chemical Abstracts Service Registry No.: 1069-55-2*

Therapeutic Category: Surgical aid (tissue adhesive)*

LAIR Code: TP60

Chemical structure:



Molecular formula: $C_8H_{11}NO_2$

Molecular weight: 153.18

Physical state: Clear Colorless Liquid

Boiling point: 170°C*

Stability: Stable in sealed ampules. Polymerizes within minutes in contact with air. Polymerizes in less than 1 second on contact with ionic solutions, e.g., saline or blood.*

Name of contaminants and percentages: Chemical data sheet attached.

Source: Ethicon, Inc.
Somerville, New Jersey 08876

Lot No.: 929-252

Analytical data/purity: Infrared spectrophotometry was performed on 11, 23, and 25 Jan 84 † and the results were identical to the standard spectrum from Ethicon, Inc. Major absorption peaks were observed at 2965, 1740, 1470, 1385, 1290, 1190, 980, 930, and 715cm^{-1}.

Analytical Data/
Stability: Samples of isobutyl 2-cyanoacrylate (IBC) were evaluated by gas chromatography on 11, 23, and 25 Jan 84.† Thus, IBC was analyzed prior to dosing, on the first day of dosing and the day following dosing. The chromatogram for each analysis showed only one peak with a retention time of 3.2 min. These data support the sponsor's claim that the IBC will not deteriorate inside the sealed ampules.

---

*Windholz M. Merck Index. 10th edition, 1983. Monograph number 1433, Bucrylate. Page 201-202. Merck & Co, Inc, Rahway, NJ.

†O'Connor RJ. Memorandum for Record, Subject: Analysis report, GLP Study No. 83009, Analytical Chemistry Group. Letterman Army Institute of Research, Presidio of San Francisco, CA.

Brown--38

ETHICON

INC.

SOMERVILLE . NEW JERSEY

January 6, 1984

To: Dr. W. D. Sheffield

cc: Mrs. S. L. Couchman
Dr. A. W. Fetter
Mr. J. P. O'Donnell
Dr. D. W. Regula

Subject: BUCRYLATE TISSUE ADHESIVE
TUMORGENICITY STUDY

The following material is being transmitted to you for initiation of the tumorgenicity study:

Lot #929-252 (750 ampules)
0.5 ml
IBC-2

One hundred twenty-five ampules have been included for stability assurance testing and another one hundred twenty-five ampules for long-term retention as required by GLP regulations.

Attached are the finished goods test results and a reference infrared spectrum for this lot. The primary sterility run number is R315001 and the overwrap sterility run number is R343MB2.

Please let me know if I can answer any questions.

Eva Furrier

mem

Attachment

Finished Goods Test Results

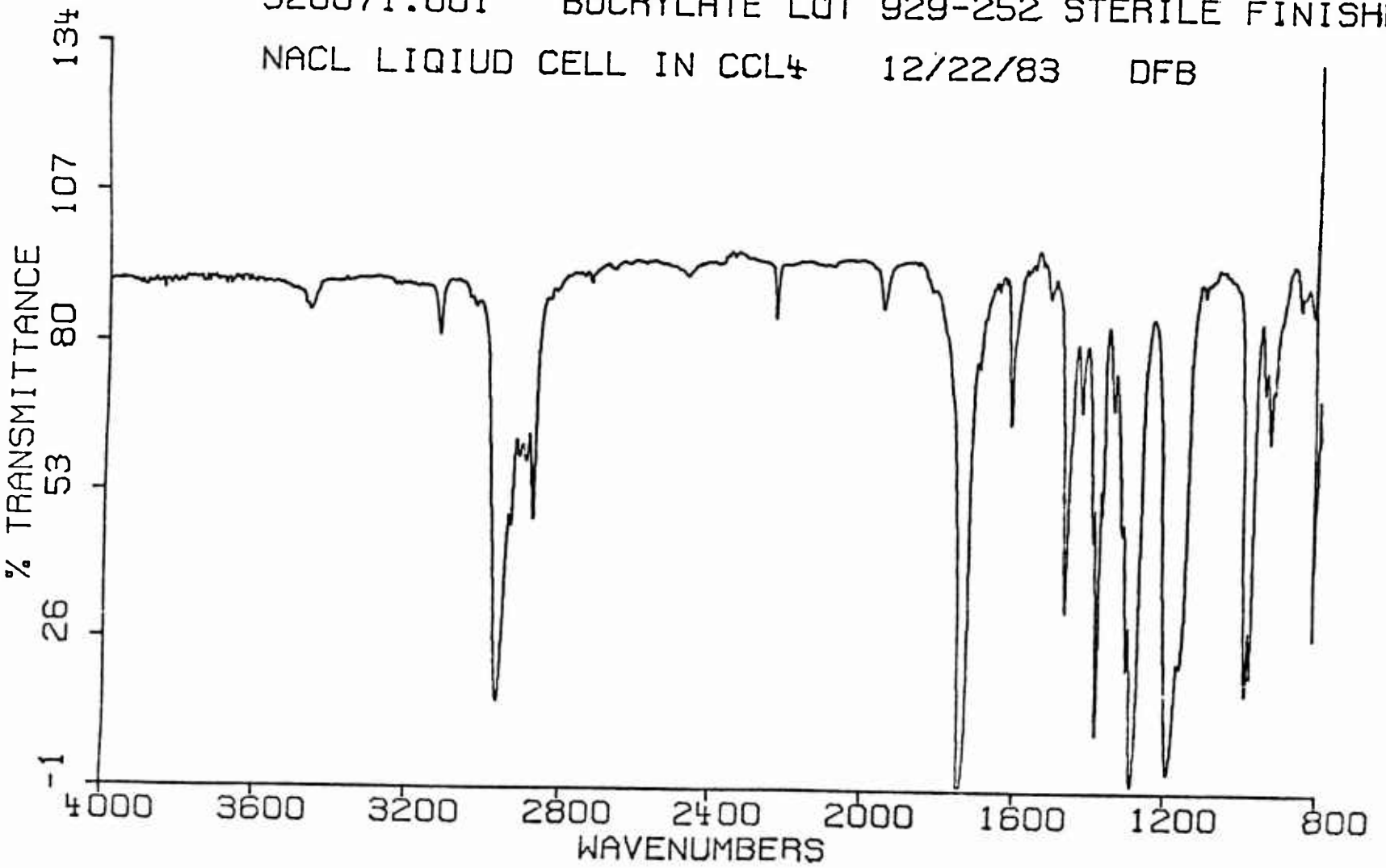
Lot #929-252

Test	Result
Identification, Infra-Red	Conforms to standard
Total Monomer, % (W/W)	99.9
SO_2, ppm (W/V)	562
Hydroquinone, % (W/W)	0.081
Isobutyl Cyanoacetate, ppm (W/W)	None detected
Color	0.046 at 400 nanometer 0.0002 from 400-800 nanometers
NIR Absorptivity, mg/absorbance unit	2.188
H_2O, ppm (W/V)	<100
Heavy Metals as Lead, ppm (W/W)	<10
Isobutanol, ppm (W/V)	725
Viscosity, cps at 30°C	2.3

Reference #929-252
Analytical Service Request #20071

S20071.001 BUCRYLATE LOT 929-252 STERILE FINISHED PRODUCT

NACL LIQIUD CELL IN CCL4 12/22/83 DFB



SR 20071
12/22/83
DFB

DEPARTMENT OF THE ARMY
LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

REPLY TO
ATTENTION OF:

SGRD-ULV-AC

26 January 1984

MEMORANDUM FOR RECORD

SUBJECT: Analysis Report, GLP Study No. 83009, Analytical Chemistry Group

Date: 26 Jan 84
Sample: IBC-2 (Isobutyl-2-cyanoacrylate)
Lot: 929-252

I. Identity

The Infrared Spectra 131, 132, 133 (11 Jan 84), 135, 136, 137 (23 Jan 84), and 138, 139, 140 (25 Jan 84) are consistent with the Infrared Spectrum provided by ETHICON (SR 20071 - 12/22/83-DFB).

Instrument: Perkin-Elmer Model 457
Red Tag 2912
FSN 6650-C19-5014

Methods: Analytical method AD-100B, identification of isobutyl-2-cyanoacrylates, analytical chemistry, ETHICON, Inc. (9/16/70), was used as the basis for analysis. The Infrared Spectra were done in two different ways. The first followed the above method with the following exceptions: KBr (potassium bromide) was used for the window material and the reference cell was a variable path length cell that was matched to the sample cell. The second method was a "Neat" film of the sample between KBr windows. The film method provided additional information including a peak near 800 cm^{-1} which was masked by the solvent in the first method.

II. Purity

The gas chromatographic profiles of IBC-2 showed one major component representation 100% of the total peak area when it was run on 11 Jan 84, 23 Jan 84, and 25 Jan 84.

Methods: Analytical method AD-100B, identification of isobutyl-2-cyanoacrylates, analytical chemistry, ETHICON, Inc. (9/16/70), was used as the basis for the analysis.

SGRD-ULV-AC 26 January 1984
SUBJECT: Analysis Report, GLP Study No. 83009, Analytical Chemistry Group

Instrument: Varian 4600

Column: 3% SP-2100 on 100/120

Injector: 200°C

Detector: 250°C

Carrier Gas: Nitrogen (20 cc/min)

Run Length: 15 minutes

Detector: FID

Sensitivity: 10-11

III. Conclusion

The above data indicate that the IBC-2, Lot 929-252, has not deteriorated in the sealed vials provided by ETHICON and is consistent with the data provided.

RICHARD J. O'CONNOR
Research Chemist
Analytical Chemistry Group

ANIMAL DATA

Species: Rattus norvegicus

Strain: Fischer-344 (CDF)

Source: Charles River Breeding Laboratories, Inc.
Wilmington, MA 01887
Reared at Kingston (K62) plant.

Sex: Male and female

Date of birth: 13 December 1983

Method of randomization: Weight biased, stratified animal allocation (RANDOM Computer Program, SOP OP-ISG-21 and SOP OP-ISG-24)

Animals in each group: 68 male and 68 female animals, except female control group totaled 67 animals

Condition of animals at start of study: Normal

Body weight range at dosing: 29 - 123 g
(male $\bar{x}$ = 94.0 g; female $\bar{x}$ = 73.8 g)

Toxicology In-Life (TOXSYS®) Identification procedures: Ear-tagging procedure (SOP-OP-ARG-1), tag numbers 84D00001 to 84D00209 (inclusive) for males and 84D00226 to 84D00435 (inclusive) for females.

Pathology Identification procedures: Animals were assigned a three digit number for data entry into the Xybion® Data Acquisition Computer. A cross reference list to the TOXSYS® numbers was generated by the LAIR Comparative Pathology Branch.

Pretest conditioning: Quarantine/acclimation 11-22 January 1984

Justification: The Fischer-344 laboratory rat has proven to be a sensitive and reliable model for chronic carcinogenesis bioassays due to its low incidence of spontaneous mammary gland and liver cancer versus the Sprague-Dawley or Charles River CD rat. This strain is recommended by the NCI Carcinogenesis Bioassay Program.

Group Codes:

Group	Toxicology Code	Pathology Code
High-Dose IBC (100 ul)	A *(Red)†	1 ǂ(High)
Low Dose IBC (10 ul)	B *(Yellow)†	2 ǂ(Low)
Saline Control (100 ul)	C *(White)†	3 ǂ(CTL)

*Alphabetic code used on 2 x 3 inch cage card and on animal's chest during surgical phase.

†Plastic cage card protector contained a barcoded animal number (84D00---) and a .5 inch square piece of color coded tape.

ǂNumerical code used to group pathology data within Xybion® computer software.

SGRD-ULV-P 30 March 1984

MEMORANDUM FOR RECORD

SUBJECT: Surgical Report, GLP Study 83009

1. On 23 & 24 January 1984 surgery was performed in the Operating Room, LAIR, on 407 six-week-old acclimated Fischer-344 rats assigned to the TSG chronic two-year Bucrylate® Carcinogenesis Bioassay. Surgeons involved were: COL Carpenter and LTC Koppelman, USAIDR and MAJ Rodkey, LAIR. Surgery was performed under LAIR GLP Protocol 83009.

2. Surgery was necessary to enable the test substance (Bucrylate®) to be applied directly to the surface of the liver of study animals. Surgery on 179 males occurred on 23 Jan and surgery on the remaining 25 males and 203 females occurred on 24 Jan 84.

3. Animals were transported, one rack of 60 rats at a time, to the ORS Surgical Suite from the TSG Animal Suite. Racks were covered with sterile sheets to provide for infection control and a dark quiet unstressed environment. Surgery started at 0730 hours on 23 Jan with animal number 84D00001 and progressed through animal numbers sequentially to 84D00434. Animals were randomly assigned to the three dose groups. Animals were presented to the surgeons in a random fashion without regard to group assignment. Animals were fasted (from food only) 1-4 hours prior to surgery.

4. Each animal was examined for health, checked to verify identification (ear tag, cage card bar code and group assignment tape) and weighed on an Arbor scale (TOXSYS® terminal recorded). The scale was recalibrated each morning prior to use. Male animals weighed approximately 100 g and females 75 g each. Anesthesia consisted of an intramuscular hindlimb injection of a mixture of xylazine HCl (10 mg/kg) and ketamine HCl (50 mg/kg). Anesthetic was prepared by LTC Rodkey by mixing: 5 ml ketamine (100 mg/cc), 2.5 ml Rompun® (20 mg/cc) and 42.5 ml of sterile saline. Dose calculations, lot and expiration of anesthetics and diluent are provided in Incl #1.

5. Proper identification and controls on group assignment for dosing was stressed. Color coded tape, with the animals' number, was placed on the tail of the animal while a "back-up system" letter signifying dose group was placed on the chest of the animal with surgical marker pen (black CMS fine tip marking pen, lot #138-800). Animals were prepared for surgery by clipping the abdomen and caudal ventral half of the thorax with a number 40 Oster blade and electric clipper.

Animal anesthesia, weighing and clipping were performed by TSG technicians under MAJ Morgan's supervision.

6. Rats were placed on a rat restraining board in the supine position and the clipped area was scrubbed with povidone-iodine surgical soap and disinfected with povidone-iodine solution and alcohol. The rats were moved to the surgery table and draped so that only the surgically prepared area was exposed. LAIR surgical operaing procedures applicable to instrument sterilization, aseptic technique, and sterile field were in effect. Surgical packs were exchanged, cleaned and autoclaved after every 6 animals. Surgeons changed gloves after every six animals, and dosing personnel changed gloves frequently.

7. A midline laparotomy incision was made extending 2-3 cm caudal from the xyphoid cartilage. The liver was exposed by the surgeon using either ophthalmic surgical retractors or by "tenting" the abdominal wall with forceps. Bucrylate® (Lot 929-252; Ethicon, Inc.) or sterile saline was applied to the surface of the exposed liver (usually caudate lobe) in amounts specified in the protocol. Dose Group 1, the high dose group, received 100 microliters (ul) of isobutyl-2-cyanoacrylate (IBC); Dose Group 2 (low dose) received 10 ul of IBC and Group 3 (control) received 100 ul of sterile isotonic saline (Lot 56-329-FD-05, Exp 1 Sep 1986; Abbott). Dosing was performed by TSG personnel using fixed volume Eppendorf micropipettes (calibrated 17 and 18 Jan 84) with sterile disposable tips. One ampule of Bucrylate® was used per animal for dose groups 1 and 2--any remaining test compound was discarded.

8. One animal (84D00126) was misdosed and removed from the study. After application of the IBC the abdominal walls were retracted or "tented" for approximately two minutes to allow for drying of the test substance. Dosing was monitored by the Principal Investigator, MAJ Brown (ID 10186).

9. The laparotomy incision was closed using two layers. The first consisted of 4-0 Vicryl® (Ethicon, Inc.) in a simple continuous pattern for the abdominal fascia, muscle and peritoneum. The skin was closed using either 35 mm Proximate® (Ethicon, Inc.) skin staples or 35 mm Michell skin clips.

10. Animals were recovered in clean rat rack cages in the autoclave room adjoining the Surgical Suite. Temperatures in the recovery area were warm and averaged approximately 29.1-31.9°C. After approximately 2 hours in the recovery area, the animals were transferred back to the TSG Animal Suite (RS1419) and given water and food.

11. Animals were monitored postoperatively by LTC Rodkey and TSG staff. Skin staples were removed on 31 Jan and 1 Feb 84 (7-10 days) by TSG veterinarions. Twelve of the 407 rats died or were removed from the study during the first week after surgery due to underweight condition, surgical complications and/or obstructed intestine due to

Bucrylate® adhesions. Postoperatively, rat #84D0C013 acquired an infection along the line of incision. After one week of treatment with H_2O_2 the incision healed. Approximately 50 animals were noted to have corneal opacities one week postoperatively. Keratitis sicca (dry eye) and subsequent ulcerative keratitis is a fairly common sequela to rat surgery. The etiology is thought to be related to drying of the cornea as the globe protrudes, and under anesthesia, the eyelids fail to cover the cornea and the blink reflex is absent.

12. Overall the surgery went very smoothly and animals tolerated the procedure well. On 1 Feb 84, 382 animals had recovered--the initial goal was to have at least 360 survivors for the study.

13. Personnel assisting in the surgery are listed in Incl #2. Study records are on file listing by animal the amounts of anesthesia administered, surgeon and dosing personnel. Ms. Janice M. Adams, Manager, Regulatory Affairs, Ethicon, Inc., audited the surgery on 23 & 24 Jan 84. CPT Carroll, LAIR, QAO also visited the Surgical Suite during this period.

14. In preparation for surgery, a meeting was held between ORSG and TSG personnel on 13 Jan 84. The Ethicon videotape on the surgical procedure was reviewed and technicians practiced the dosing procedure using Eppendorf micropipettes and one ampule of Bucrylate®. Pilot surgery was performed on 20 Jan 84. Eighteen rats were operatively laparotomized and dosed according to simulated group assignments.

Incl
as

WILLIAM G. RODKEY, DVM
LTC, VC
Chief, Operating Room Services Group

CF:
COL Carpenter
LTC Koppelman
MAJ Korte
Rawdata Binder, 83009

Enclosure One to Surgical Memorandum For Record, 30 March 1984

ANESTHESIA GLP STUDY 83009

RAT WT	10 mg/cc Xylazine (Rompun®)*	100 mg/cc Ketamine (Vetalar®)†	VOL MIXTURE
80 g	0.4 mg	4 mg	0.4 ml
100 g	0.5 mg	5 mg	0.5 ml
120 g	0.6 mg	6 mg	0.6 ml
140 g	0.7 mg	7 mg	0.7 ml

Vial mixture has 10 mg ketamine xylazine (Rompun®)/ml

UN

Xylazine (Rompun®)	10 mg/kg; 20 mg/cc	(Lot 260013, Jan 85 Exp.)
Ketamine	50 mg/kg; 100 mg/cc	(Lot 03793p, Jul 88 Exp.)
Saline Diluent‡		(Lot 7C856X9, Nov 84 Exp.)

Mixture: 5 ml ketamine + 2.5 ml xylazine + 42.5 ml saline = 50 ml

* Rompun®, Haver-Lockart, Shawnee, KS.
† Vetalar®, Parke-Davis, Morris Plains, NJ.
‡ Viaflex®, 0.9% NaCl Injection USP, Travenol Laboratories, Inc., Deerfield, IL.

Enclosure Two to Surgical Memorandum For Record, 30 March 1984

LAIR PERSONNEL WORKING ON SURGICAL PHASE OF GLP STUDY 83009

Personnel	Group	Duty
MAJ Korte, Don W. Jr	Toxicology	Study Director
MAJ Brown, Larry D.	Toxicology	Principal Investigator
MAJ Morgan, Earl W.	Toxicology	TOXSYS®, Presurgery Prep, Recovery
SFC Farmer, Charles N.	Toxicology	Scheduling
SP5 Kellner, Thomas P.	Toxicology	Dosing
SP5 Mullen, Lawrence	Toxicology	Dosing
SP5 Rodriquez, Justo	Toxicology	Prep
PFC Sano, Steven K.	Toxicology	Prep, Late Night Recovery
Ms. Lewis, Carolyn M.	Toxicology	Dosing
Ms. Coppes, Valerie G.	Toxicology	Initial Recovery, Prep,
Mr. Dacey, John	Toxicology	Dosing
Mr. Spieler, Richard A.	Toxicology	Primary Animal Caretaker
Ms. Hernandez, Susan	Toxicology	TOXSYS, Prep
Mr. Sands, Edward M.	Toxicology	Prep
LTC Rodkey, William G.	Operating Rm	Surgery
SSG Del la Cerda, Maria V.	Operating Rm	Surgery
SSG Davis, Garry	Operating Rm	Surgery
SP5 Weber, David	Operating Rm	Surgery
SP5 Aiken, Byron	Operating Rm	Surgery
SP5 Cornier-Garcia Juan	Operating Rm	Surgery
SP5 Stevens, Daniel	Operating Rm	Surgery
SP4 Peterson, Kimothy	Operating Rm	Surgery
PFC Rothhammer, Gregory A.	ARG	Prep

HISTORICAL LISTING OF STUDY EVENTS

Date	Event
11 Jan 84	209 male and 209 female Charles River (CDF) Fischer-344 rats were received. Animals were checked for physical condition, sexed, individually caged, and fed.
12 Jan 84	Rats were ear-tagged and weighed. Eight rats (4 male and 4 female) were submitted for necropsy quality control.
11-22 Jan 84	Animals were observed daily during quarantine/acclimation period.
19 Jan 84	Animals were weighed and randomized into dose groups.
20 Jan 84	Three underweight animals and one maloccluded animal were sacrificed.
23 Jan 84-29 Jan 85	All animals were observed twice daily throughout the study for clinical signs and mortality.
23 Jan 84	One hundred seventy-nine animals were weighed, provided with ketamine/Rompun® anesthesia, surgically laparotomized, and implanted with IBC or saline according to dose group.
24 Jan 84	Two hundred twenty-eight animals were weighed, provided with ketamine/Rompun® anesthesia, surgically laparotomized, and implanted with IBC or saline according to dose group.
24 Jan- 1 Feb 84	All animals were observed frequently during this 7-day postoperative recovery period.

Date	Event
24,25,26,27, or 28 Jan 84	Twenty-five animals either died or were sacrificed during the postoperative period because of complications or underweight conditions.
1 Feb 84	Three hundred seventy-eight (92.8%) of 407 rats that went to surgery remained on study.
3 Feb 84 - 27 Jan 85	Seventeen unscheduled animals were necropsied during first year of study -- 14 sacrificed due to poor condition and 3 died in cage.
3,31 Mar, 8 Apr, 9,18,19,27 Jun, 14,16 Jul,15 Sep, and 13 Dec 84	Steam outages occurred or animal suite ventilation fans down. Spikes in relative humidity and small drops in room temperature occurred during these periods.
12,19,23 or 24 Jan 84 28 or 29 Jan 85	All animals were weighed.
16 or 17 Feb 15 or 16 Mar 12 or 13 Apr 10 or 11 May 7 or 8 Jun 5 or 6 Jul 2 or 3 Aug 30 or 31 Aug 27 or 28 Sep 25 or 26 Oct 22 or 23 Nov 20 or 21 Dec 84 and 17 or 18 Jan 85	All animals were examined, palpated by veterinarian, or toxicologist and weighed at 28-day intervals (monthly).
28-29 Jan 85	Interim Sacrifice. Sixty animals were weighed, sacrificed, and necropsied.
30 Jan 85	Three hundred five rats remain "on study" for second year of study.

Clinical Sign Summary Reports

(Glossary of Terminology Included at Volume 2, Part 2, Appendix H; certain related clinical signs were grouped to facilitate summarization in Appendix E -- see below for groupings)

Clinical Sign Grouping/Summary Categories For Appendix E.

1. Corneal opacity includes corneal edema and/or ulceration.

2. Conjunctivitis or ocular discharge includes lacrimation or chromodacryorrhea.

3. Anterior body stain includes red nasal discharge, red stain/coloration around mouth, nose or front legs/paws/chest.

4. Posterior body stain includes staining of perianal, tail or abdominal areas.

5. Respiratory dysfunction includes increased respiratory rate, decreased respiratory rate, rales, wheezing and/or tachypnea.

6. Xyphoid protuberance includes xyphoid nodule.

7. Eartag reaction/infection includes ulceration, scab, edema, irritation, hair loss around tag and/or bleeding associated with the ear.

8. Postoperative complication includes infected suture line, hernia of incision, suture line swollen/raised and/or skin staple/clip problem.

9. Ocular abnormality includes hyphemia, prolapsed, luxated or opaque lens, exophthalmos, mydriasis, dilated pupil, iris abnormality/iritis, ocular edema not specific to cornea, and ulcerated eye.

10. Reproductive tract dysfunction (male) includes preputial gland fistula/abscess or penile erythema.

11. Reproductive tract dysfunction (female) includes perivaginal fistula/abscess or vaginal discharge.

Frequency of Clinical Observations
Unscheduled Males (4)
IBC Carcinogenicity Bioassay

Clinical Sign	High Dose (N=3)	Low Dose (N=1)	Control (N=0)	Totals
Corneal Opacity	1	1	0	2
Anterior Body Stain	1	1	0	2
Dehydration	1	0	0	1
Respiratory Dysfunction	0	1	0	1
Xyphoid Protuberance	1	1	0	2
Intra-abdominal Mass	1	0	0	1
Gastrointestinal Dysfunction	1	0	0	1
Subcutaneous Abscess	1	0	0	1
Died in Cage (Death)	0	1	0	1

Frequency of Clinical Observations
Unscheduled Females (13)
IBC Carcinogenicity Bioassay

Clinical Sign	High Dose (N=7)	Low Dose (N=3)	Control (N=3)	Totals
Conjunctivitis or Ocular Discharge	6	2	3	11
Corneal Opacity	5	3	0	8
Anterior Body Stain	3	2	1	6
Posterior Body Stain	3	0	2	5
Ear Tag Reaction/Infection	3	0	2	5
Dehydration	3	0	0	3
Respiratory Dysfunction	2	1	1	4
Cutaneous Scab, Hind Leg	1	0	1	2
Rough Coat	1	0	2	3
Alopecia	0	1	1	2
Hypotonia	1	1	0	2
Poor Condition/Emaciated	0	1	1	2
Scaling Tail	1	0	0	1
Cutaneous Erythema	0	1	1	2
Intra-abdominal Mass	3	0	1	4
Died in Cage (Death)	2	0	0	2

Frequency of Clinical Observations
Scheduled Males (30)
IBC Carcinogenicity Bioassay

Clinical Sign	High Dose (N=10)	Low Dose (N=10)	Control (N=10)	Totals
Normal	6	1	4	11
Conjunctivitis or Ocular Discharge	0	2	0	2
Corneal Opacity	1	2	0	3
Anterior Body Stain	2	5	3	10
Ear Tag Reaction/Infection	1	2	3	6
Xyphoid Protuberance	2	1	1	4
Irritable	0	1	0	1
Postoperative Complications	1	0	2	3
Intra-abdominal Mass	1	2	0	3
Inactivity	1	0	0	1

Frequency of Clinical Observations
Scheduled Females (30)
IBC Carcinogenicity Bioassay

Clinical Sign	High Dose (N=10)	Low Dose (N=10)	Control (N=10)	Totals
Conjunctivitis or Ocular Discharge	9	10	10	29
Corneal Opacity	9	8	8	25
Ocular Abnormality	1	0	0	1
Anterior Body Stain	2	5	3	10
Posterior Body Stain	2	4	3	9
Ear Tag Reaction/Infection	7	6	7	20
Dehydration	2	1	1	4
Respiratory Dysfunction	2	4	0	6
Cutaneous Scab Hind Leg	2	1	0	3
Xyphoid Protuberance	1	0	1	2
Rough Coat	1	1	0	2
Alopecia	1	2	1	4
Hunched Posture	1	1	0	2
Intra-abdominal Mass	1	0	0	1
Reproductive Tract Dysfunction	0	1	0	1
Postoperative Complication	1	0	0	1
Self-mutilation	0	1	0	1
Cutaneous Scab, Head	0	1	0	1

Frequency of Clinical Observations
First-Year Survivor Males (162)
IBC Carcinogenicity Bioassay

Clinical Sign	High Dose (N=50)	Low Dose (N=55)	Control (N=57)	Totals
Normal	11	25	20	56
Conjunctivitis or Ocular Discharge	4	2	9	15
Corneal Opacity	19	4	7	30
Ocular Abnormality	0	3	2	5
Anterior Body Stain	22	18	21	61
Posterior Body Stain	6	0	0	6
Ear Tag Reaction/Infection	7	12	12	31
Dehydration	11	1	3	15
Respiratory Dysfunction	3	1	1	5
Cutaneous Scab, Hind Leg	1	0	0	1
Xyphoid Protuberance	3	2	0	5
Rough Coat	5	0	0	5
Irritable	2	0	1	3
Alopecia	0	0	1	1
Hunched Posture	2	0	1	3
Reproductive Tract Abnormality	1	0	1	2
Nasal Papilloma	0	0	1	1
Scab Head	1	0	0	1
Postoperative Complication	0	1	0	1
Intra-abdominal Mass	1	0	0	1
Inactivity	3	0	1	4

Frequency of Clinical Observations
First-Year Survivor Females (143)
IBC Carcinogenicity Bioassay

Clinical Sign	High Dose (N=40)	Low Dose (N=52)	Control (N=51)	Totals
Conjunctivitis or Ocular Discharge	37	49	50	136
Corneal Opacity	36	47	45	128
Ocular Abnormality	3	3	3	9
Anterior Body Stain	17	15	12	44
Posterior Body Stain	23	15	22	60
Ear Tag Reaction/Infection	12	24	31	67
Dehydration	14	2	1	17
Respiratory Dysfunction	6	6	14	26
Cutaneous Scab, Hind Leg	3	4	2	9
Xyphoid Protuberance	0	1	1	2
Rough Coat	3	1	1	5
Irritable	2	0	0	2
Alopecia	2	3	2	7
Hunched Posture	1	0	0	1
Malocclusion, Incisors	0	0	1	1
Poor Condition/Emaciated	0	1	2	3

LETTERMAN ARMY INSTITUTE OF RESEARCH
DIV OF RES SUPP, PATH SERV GP
PRESIDIO OF SAN FRANCISCO, CA 94129
SPECIES: RAT/FISCHER-344

INCIDENCE SUMMARY REPORT FOR GROSS NECROPSY OBSERVATIONS
STUDY NUMBER: GLP83009
REPORT FOR UNSCHEDULED DEATHS: DAY -3 TO DAY 2 OF STUDY
STUDY START DATE: 27-JAN-84

PRINTED: 24-JAN-86
PAGE: 1
STUDY TYPE:

NOTE: CTLS = CONTROLS
FROM GROUP(S): 3

ANIMAL SEX:	-- MALES --			-- FEMALES --		
GROUP:	CTLS	1	2	CTLS	1	2
NO. IN GROUP:	1	5	2	3	11	3
WHOLE BODY						
NO GROSS LESIONS RECOGNIZED	1	0	0	1	0	0
POST MORTEM AUTOLYSIS.	0	1	0	0	0	0
VASCULAR SYSTEM.	0	1	0	0	0	0
PERINEUM	0	0	0	0	1	0
MOUTH	0	0	0	0	1	0
TOTAL:	1	2	0	1	2	0
CECUM						
TWISTED	0	1	0	0	0	0
SUTURED TO ABDOMINAL INCISION	0	1	0	0	0	0
TOTAL:	0	2	0	0	0	0
COLON						
ADHERED TO LIVER.	0	1	0	0	1	0
TEST COMPOUND	0	1	0	0	0	0
TOTAL:	0	2	0	0	1	0
PLEURAL CAVITY						
FLUID-FILLED	0	1	0	0	0	0
TOTAL:	0	1	0	0	0	0
PERITONEAL CAV.						
ADHESION(S)	0	1	0	0	1	0
FLUID-FILLED	0	1	0	0	1	0
SMALL INTESTINE	0	2	1	1	3	0
LARGE INTESTINE	0	0	0	0	2	1
TEST MATERIAL	0	1	0	0	1	0
TOTAL:	0	5	1	1	8	1
EYES & OPTIC N.						
RETINAL HEMORRHAGE	0	0	0	1	0	0
TOTAL:	0	0	0	1	0	0
ILEUM						
DISTENDED WITH INGESTA	0	1	0	0	0	0
SUTURED TO ABDOMINAL INCISION	0	1	0	0	0	0
TOTAL:	0	2	0	0	0	0
JEJUNUM						
ADHERED TO LIVER.	0	0	0	0	1	0
DILATED	0	1	0	0	1	0
DILATED AND RED	0	1	0	0	0	0
TOTAL:	0	2	0	0	2	0

NOTE: CTLS = CONTROLS
FROM GROUP(S): 3

ANIMAL SEX:	-- MALES --			-- FEMALES --		
GROUP:	CTLS	1	2	CTLS	1	2
NO. IN GROUP:	1	5	2	3	11	3
LIVER						
ADHERED TO DIAPHRAGM.	0	4	1	0	8	1
ADHERED TO DIAPHRAGM AND STOMACH	0	0	0	0	0	1
ADHERED-DIAPHRAGM & PERITONEUM.	0	0	0	0	3	0
FOCI	0	0	0	1	1	1
TOTAL:	0	4	1	1	12	3
LUNGS						
CONGESTED / RED	0	0	0	0	1	0
TOTAL:	0	0	0	0	1	0
PAWS/FEET						
RED/BROWN CRUSTY MATERIAL.	0	1	0	0	1	0
TOTAL:	0	1	0	0	1	0
SKIN						
SUBCUTANEOUS	0	0	0	0	1	0
INCISION SITE	0	1	1	0	0	1
HAIR, RED/BROWN CRUSTY MATERIAL.	0	1	0	0	0	0
ABSCESS(ES)	0	1	0	0	0	0
TOTAL:	0	3	1	0	1	1
STOMACH						
DILATED	0	0	0	0	2	0
ADHERED TO LIVER.	0	0	0	0	1	0
TOTAL:	0	0	0	0	3	0
URINARY BLADDER						
ABNORMAL URINE	0	0	1	0	0	0
TOTAL:	0	0	1	0	0	0

LETTERMAN ARMY INSTITUTE OF RESEARCH
DIV OF RES SUPP, PATH SERV GP
PRESIDIO OF SAN FRANCISCO, CA 94129
SPECIES: RAT/FISCHER-344

INCIDENCE SUMMARY REPORT FOR GROSS NECROPSY OBSERVATIONS
STUDY NUMBER: GLP83009
REPORT FOR UNSCHEDULED DEATHS: DAY 3 TO DAY 367 OF STUDY
STUDY START DATE: 27-JAN-84

PRINTED: 24-JAN-86
PAGE: 1
STUDY TYPE:

NOTE: CTLS = CONTROLS
FROM GROUP(S): 3

ANIMAL SEX:	-- MALES --			-- FEMALES --		
GROUP:	CTLS	1	2	CTLS	1	2
NO. IN GROUP:	0	3	1	3	7	3
WHOLE BODY						
PERINEUM	0	0	0	0	1	0
CHIN	0	0	0	0	0	1
EMACIATED	0	0	0	0	0	1
SKIN	0	0	0	0	3	0
SUBCUTANEOUS	0	0	0	0	1	0
TOTAL:	0	0	0	0	5	2
ADRENAL						
CONGESTED / RED	0	0	0	1	0	0
TOTAL:	0	0	0	1	0	0
PERITONEAL CAV.						
ADHESION(S)	0	0	0	0	1	0
FLUID-FILLED	0	0	0	0	1	0
SMALL INTESTINE	0	3	0	0	3	0
LARGE INTESTINE	0	0	0	1	0	0
MESENTERY	0	0	0	1	0	0
TOTAL:	0	3	0	2	5	0
EYES & OPTIC N.						
OCCULAR DISCHARGE	0	0	0	0	1	1
CORNEAL OPACITY	0	0	0	0	1	2
CONJUNCTIVITIS	0	0	0	1	0	0
TOTAL:	0	0	0	1	2	3
HEART						
GROWTH(S) / MASS(ES)	0	0	1	0	0	0
TOTAL:	0	0	1	0	0	0
KIDNEY						
FOCI	0	0	0	1	0	0
TOTAL:	0	0	0	1	0	0
LIVER						
ADHERED TO DIAPHRAGM.	0	2	0	0	3	2
ADHERED TO DIAPHRAGM AND STOMACH	0	0	0	0	2	0
ADHERED-DIAPHRAGM & PERITONEUM.	0	1	0	0	2	1
ADHERED TO PERITONEAL WALL	0	0	1	0	0	0
PROMINENT LOBULAR MARKINGS	0	0	0	1	0	0
ROUNDED EDGES	0	0	0	1	0	0
TOTAL:	0	3	1	2	7	3
LYMPH NODES						
ENLARGED	0	0	0	0	1	0
TOTAL:	0	0	0	0	1	0

NOTE: CTLS = CONTROLS

ANIMAL SEX:	-- MALES --			-- FEMALES --		
FROM GROUP(S): 3 GROUP:	CTLS	1	2	CTLS	1	2
NO. IN GROUP:	0	3	1	3	7	3
OVARIES						
HEMORRHAGE(S)				0	1	0
TOTAL:	0	0	0	0	1	0
PAWS/FEET						
RED/BROWN CRUSTY MATERIAL.	0	1	0	0	0	0
TOTAL:	0	1	0	0	0	0
PITUITARY GLAND						
CYST(S)	0	0	0	0	1	0
TOTAL:	0	0	0	0	1	0
SPLEEN						
ENLARGED (SPLENOMEGALY)	0	0	0	1	1	0
WHITE FOCI	0	0	1	0	0	0
TOTAL:	0	0	1	1	1	0
STOMACH						
DILATED	0	1	0	0	0	0
TOTAL:	0	1	0	0	0	0
THYROID GLANDS						
PALE AND / OR TAN COLOR	0	0	0	1	0	0
TOTAL:	0	0	0	1	0	0

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SPECIES: RAT/FISCHER-344

INCIDENCE SUMMARY REPORT FOR GROSS NECROPSY OBSERVATIONS
STUDY NUMBER: GLP83009
REPORT FOR INTERIM SACRIFICE NUMBER 1
STUDY START DATE: 27-JAN-84

PRINTED: 24-JAN-86
PAGE: 1

NOTE: CTLS = CONTROLS FROM GROUP(S): 3

STUDY TYPE:

ANIMAL SEX:	-- MALES --		
GROUP:	CTLS	1	2
NO. IN GROUP:	10	10	10
WHOLE BODY			
NO GROSS LESIONS RECOGNIZED	4	0	1
TOTAL:	4	0	1
EYES & OPTIC N.			
FOCAL CORNEAL OPACITY	1	0	1
IRREGULAR EYE SURFACE.	3	1	2
CORNEAL OPACITY	0	0	1
TOTAL:	4	1	4
LIVER			
ADHERED TO DIAPHRAGM.	2	7	5
ADHERED TO DIAPHRAGM AND STOMACH	0	1	0
ADHERED TO OMENTUM.	0	2	2
ADHERED-DIAPHRAGM & PERITONEUM.	0	0	1
ADHERED TO PERITONEAL WALL	0	0	1
PROMINENT LOBULAR MARKINGS	1	0	0
TOTAL:	3	10	9
SKIN			
CYST(S)	0	1	0
INCISION SITE	1	0	1
TOTAL:	1	1	1

NOTE: CTLS = CONTROLS FROM GROUP(S): 3

ANIMAL SEX:	-- FEMALES --		
GROUP:	CTLS	1	2
NO. IN GROUP:	10	10	10
WHOLE BODY			
NO GROSS LESIONS RECOGNIZED	4	0	0
TOTAL:	4	0	0
CECUM			
MASS(ES)	0	1	0
ADHERENT TO OTHER ORGANS	0	1	0
TOTAL:	0	2	0
PERITONEAL CAV.			
ADHESION(S)	0	1	0
TOTAL:	0	1	0
EYES & OPTIC N.			
FOCAL CORNEAL OPACITY	0	4	1
IRREGULAR EYE SURFACE.	1	3	6
CORNEAL DISCOLORATION.	0	1	0
OCCULAR DISCHARGE	1	1	1
CORNEAL OPACITY	2	0	4
TOTAL:	4	9	12
ILEUM			
DILATATION	0	1	0
TOTAL:	0	1	0
JEJUNUM			
FIBROUS ADHESIONS (TAGS)	0	1	0
TOTAL:	0	1	0
KIDNEY			
CYST	0	0	1
TOTAL:	0	0	1
LIVER			
FIBROUS ADHESIONS (TAGS)	0	1	0
ADHERED TO DIAPHRAGM.	0	3	3
ADHERED TO DIAPHRAGM AND STOMACH	0	2	0
ABSCESS(ES)	0	1	0
ADHERED-DIAPHRAGM & PERITONEUM.	0	2	2
ADHERED TO PERITONEAL WALL	0	1	2
FOCI	1	0	0
TOTAL:	1	10	7
OVARIES			
CYST(S) WITHIN OVARY	0	0	1
TOTAL:	0	0	1

NOTE: CTLS = CONTROLS ANIMAL SEX: -- FEMALES --
FROM GROUP(S): 3 GROUP: CTLS 1 2
NO. IN GROUP: 10 10 10

SPLEEN			
PROMINENT FIBROUS CAPSULE	0	1	0
ENLARGED (SPLENOMEGALY)	0	1	0
TOTAL:	0	2	0
STOMACH			
GROWTH(S) / MASS(ES)	0	1	0
TOTAL:	0	1	0
UTERUS			
HYDROMETRA	1	1	0
THICKEN	1	0	0
POLYP	0	0	1
TOTAL:	2	1	1

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SPECIES: RAT/FISCHER-344

INCIDENCE SUMMARY OF MICROSCOPIC OBSERVATIONS(ALL FINDING)
STUDY NUMBER: GLP83009
PATHOLOGIST(S): MELLICK, PAUL W., Smith, Catherine D
STUDY START DATE: 23-JAN-84

PRINTED: 30-JAN-86
PAGE: 1

STUDY TYPE: CHRONIC/2 YR CARCINOGENIC

NOTES: ANIMALS = UNSCHEDULED DEAD FROM 29-JAN-84 TO 27-JAN-85
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S	ANIMAL S E X: / DOSAGE GROUP: / NO. IN GROUP:	A N I M A L S A F F E C T E D -- -- MALES -- CTLS	1	2	-- FEMALES -- CTLS	1	2
BRAIN	NUMBER EXAMINED:	0	3	1	3	7	3
TRACHEA	NUMBER EXAMINED:	0	3	1	3	7	3
THYROID GLANDS	NUMBER EXAMINED:	0	3	1	3	7	3
PARATHYROID	NUMBER EXAMINED:	0	2	1	3	6	2
ESOPHAGUS	NUMBER EXAMINED:	0	3	1	3	7	3
SALIVARY GLAND	NUMBER EXAMINED:	0	3	1	3	7	3
LACRIMAL GLAND	NUMBER EXAMINED:	0	3	1	3	6	3
EXORBITAL LACRIM	NUMBER EXAMINED:	0	3	1	3	7	3
HEART	NUMBER EXAMINED:	0	3	1	3	7	3
-CARDIOMYOPATHY		0	0	0	0	0	0
-M- ATRIO CAVAL EPITHELIAL MESOTHELIOMA		0	0	1	0	0	0
AORTA	NUMBER EXAMINED:	0	3	1	3	7	3
LUNGS	NUMBER EXAMINED:	0	3	1	3	7	3
-HYPERPLASTIC NODULE		0	0	0	0	0	0
-PLEURITIS WITH SUBADJACENT CHRONIC PNEUMONIA		0	0	0	0	0	0
-PULMONARY EDEMA		0	0	1	0	0	0
-VASCULAR CONGESTION		0	0	1	0	0	0
THYMUS	NUMBER EXAMINED:	0	3	1	2	6	3
-PLEURITIS		0	0	0	0	0	0
SPLEEN	NUMBER EXAMINED:	0	3	1	3	7	3
-LYMPHOID HYPERPLASIA OF THE SPLENIC CORPUSCLES		0	0	0	0	0	0
-FIBROSIS CAPSULAR		0	0	0	0	0	0
-INFARCTION		0	0	0	1	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = UNSCHEDULED DEAD FROM 29-JAN-84 TO 27-JAN-85
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S	ANIMAL S E X: / DOSAGE GROUP: / NO. IN GROUP:	-- A N I M A L S A F F E C T E D -- -- MALES -- CTLS	1	2	-- FEMALES -- CTLS	1	2
LYMPH NODES	NUMBER EXAMINED:	0	3	1	3	7	3
-LYMPHOID HYPERPLASIA		0	0	0	0	0	0
LIVER	NUMBER EXAMINED:	0	3	1	3	7	3
-CAPSULAR FOREIGN GRANULOMATOUS REACTION		0	3	1	0	-7	-3
-BILE DUCTULE EPITHELIAL HYPERPLASIA		0	1	1	1	4	0
-HEPATITIS		0	0	0	0	1	1
-FOCUS BASOPHILIC		0	0	0	0	0	0
-HEPATOCYTIC VACUOLIZATION		0	0	0	0	0	0
-TELANGIECTASIS		0	0	0	0	0	0
-NECROSIS		0	1	0	0	0	0
-FIBROSIS CAPSULAR NO COMPOUND		0	0	0	0	0	0
-FOCUS CLEAR		0	0	0	0	0	0
-M- MONONUCLEAR CELL LEUKEMIA		0	0	0	1	1	0
KIDNEY	NUMBER EXAMINED:	0	3	1	3	7	3
-PROGRESSIVE RENAL DISEASE		0	1	0	1	2	1
URINARY BLADDER	NUMBER EXAMINED:	0	3	1	2	6	3
UTERUS	NUMBER EXAMINED:				3	7	3
-COMPOUND PRESENT WITH REACTION					0	0	0
-DILATATION OF THE UTERINE LUMEN (HYDROMETRA)					0	0	0
-PYOMETRA					0	0	0
-ENDOMETRIAL STROMAL POLYP					0	0	0
PROSTATE	NUMBER EXAMINED:	0	2	1			
-ACUTE SUPPURATIVE PROSTATITIS		0	0	0			
-CHRONIC PROSTATITIS		0	0	0			
COAG GL	NUMBER EXAMINED:	0	2	1			
SEMINAL VESICLE	NUMBER EXAMINED:	0	3	1			
EDIDIDYMIS	NUMBER EXAMINED:	0	2	1			

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = UNSCHEDULED DEAD FROM 29-JAN-84 TO 27-JAN-85
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S	ANIMAL S E X:	-- A N I M A L S A F F E C T E D --					
		-- MALES --			-- FEMALES --		
	DOSAGE GROUP:	CTLS	1	2	CTLS	1	2
	NO. IN GROUP:	0	3	1	3	7	3
TESTES	NUMBER EXAMINED:	0	3	1			
-TUBULAR ATROPHY		0	0	0			
-INTERSTITIAL CELL HYPERPLASIA		0	0	0			
-B-MESOTHELIOMA		0	0	0			
OVARIES	NUMBER EXAMINED:				3	7	3
DUODENUM	NUMBER EXAMINED:	0	3	1	3	7	3
-COMPOUND-RELATED REACTION WITH ASSOCIATED INFLAMMATION		0	0	0	0	1	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0	0	0	0
JEJUNUM	NUMBER EXAMINED:	0	3	1	3	7	2
-COMPOUND-RELATED INFLAMMATORY REACTION		0	0	0	0	0	0
-ACUTE PERITONITIS		0	0	0	0	0	0
-TO AUTOLYZED TO TELL ORIGIN		0	0	0	0	0	0
ILEUM	NUMBER EXAMINED:	0	3	1	3	6	3
-COMPOUND-RELATED INFLAMMATORY REACTION		0	1	0	0	1	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0	0	0	0
PANCREAS	NUMBER EXAMINED:	0	3	1	3	7	3
-PERITONITIS		0	1	0	0	1	0
-ACINAR (EXOCRINE) ATROPHY		0	0	0	0	0	1
CECUM	NUMBER EXAMINED	0	1	1	3	7	3
-COMPOUND-RELATED INFLAMMATORY REACTION		0	0	0	0	1	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0	0	0	0
RECTUM	NUMBER EXAMINED:	0	2	1	2	4	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0	0	0	0
COLON	NUMBER EXAMINED:	0	3	1	3	7	3
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0	0	0	0
-COMPOUND PRESENT WITH INFLAMMATORY REACTION		0	0	0	0	0	0
STOMACH	NUMBER EXAMINED:	0	3	1	3	7	3
-VILLUS ATROPHY AND/OR AUTOLYSIS		0	0	0	0	0	0
-COMPOUND-RELATED INFLAMMATORY REACTION		0	0	0	0	1	0
-SEROSAL FIBROSIS		0	0	0	0	0	0
-GLANDULAR CYST(S)		0	0	0	0	0	0

NOTES: ANIMALS = UNSCHEDULED DEAD FROM 29-JAN-84 TO 27-JAN-85
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S		-- A N I M A L S A F F E C T E D -- -- MALES --			-- FEMALES --		
ANIMAL S E X:							
DOSAGE GROUP:		CTLS	1	2	CTLS	1	2
NO. IN GROUP:		0	3	1	3	7	3
STOMACH	NUMBER EXAMINED:	0	3	1	3	7	3
-SEVERE AUTOLYSIS		0	0	0	0	0	0
SKELETAL MUSCLE	NUMBER EXAMINED:	0	3	1	3	7	3
-ACUTE MYOSITIS		0	0	0	0	0	0
SCIATIC NERVE	NUMBER EXAMINED:	0	3	1	3	7	3
TONGUE	NUMBER EXAMINED:	0	2	1	3	5	1
SKIN	NUMBER EXAMINED:	0	3	1	3	7	3
-COMPOUND PRESENT WITH ASSOCIATED INFLAMMATION\FIBROSIS		0	0	0	0	1	0
-INFLAMMATORY EXUDATE ON SKIN SURFACE		0	0	0	0	0	0
-PROCEDURE RELATED GRANULOMATOUS CELLULITIS SUBCUTIS		0	0	0	0	1	0
-NON-SUPPURATIVE DERMATITIS		0	0	0	0	0	1
MAMMARY GLANDS	NUMBER EXAMINED:	0	0	1	2	5	1
-HYPERPLASIA AND/OR HYPERTROPHY OF THE ACINAR TISSUE		0	0	1	0	0	0
NOSE/TURBINATES	NUMBER EXAMINED:	0	3	1	3	7	3
-ACUTE INFLAMMATION		0	0	0	0	0	0
BONE, STERNUM	NUMBER EXAMINED:	0	3	1	3	5	3
BONE, FEMUR	NUMBER EXAMINED:	0	3	1	3	7	3
-HYPERPLASIA MYELOID		0	1	0	0	0	0
BONE VERT	NUMBER EXAMINED:	0	3	1	3	7	3
SPINAL CORD	NUMBER EXAMINED:	0	3	1	3	7	3
ADRENAL	NUMBER EXAMINED:	0	3	1	3	7	3
-B- CORTICAL ADENOMA		0	0	0	0	0	0
PITUITARY GLAND	NUMBER EXAMINED:	0	2	1	3	7	3
-B- ADENOMA		0	0	0	0	1	0
-CYST(S)		0	0	0	0	0	0
-HEMORRHAGE		0	0	0	0	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = UNSCHEDULED DEAD FROM 29-JAN-84 TO 27-JAN-85
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S		-- A N I M A L S A F F E C T E D --					
	ANIMAL S E X:	-- MALES --			-- FEMALES --		
	DOSAGE GROUP:	CTLS	1	2	CTLS	1	2
	NO. IN GROUP:	0	3	1	3	7	3
EYES & OPTIC N.	NUMBER EXAMINED:	0	3	1	3	7	3
-METAPLASTIC BONE SCLERAL		0	0	0	0	0	0
-CORNEAL MINERALIZATION		0	0	0	0	1	2
-PROGRESSIVE RETINAL ATROPHY		0	0	0	0	0	0
-SCLERAL MINERALIZATION		0	0	0	0	0	0
-CORNEAL PIGMENTATION		0	0	0	0	0	0
-CORNEAL VASCULARIZATION		0	0	1	0	1	1
-CHRONIC KERATITIS		0	0	0	0	2	2
-IRIDOCYCLITIS		0	0	0	0	1	0
EAR	NUMBER EXAMINED:	0	3	1	3	7	3
AUDITORY SEBACEOUS	NUMBER EXAMINED:	0	3	1	3	7	3
ABDOMINAL WALL	NUMBER EXAMINED:	0	0	0	0	0	0
-INFECTION AND INFLAMMATION SEVERE INVOLVING THE MUSCULATURE AND PERITONEAL SURFACE		0	0	0	0	0	0
THORAX	NUMBER EXAMINED:	0	0	0	0	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = INTERIM SACRIFICE 1
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S	ANIMAL S E X: / DOSAGE GROUP: / NO. IN GROUP:	-- A N I M A L S A F F E C T E D -- -- MALES -- CTLS	1	2
BRAIN	NUMBER EXAMINED:	10	10	10
TRACHEA	NUMBER EXAMINED:	10	8	10
THYROID GLANDS	NUMBER EXAMINED:	10	10	10
PARATHYROID	NUMBER EXAMINED:	8	9	8
ESOPHAGUS	NUMBER EXAMINED:	6	7	8
SALIVARY GLAND	NUMBER EXAMINED:	9	9	10
LACRIMAL GLAND	NUMBER EXAMINED:	10	10	10
EXORBITAL LACRIM	NUMBER EXAMINED:	9	10	10
HEART	NUMBER EXAMINED:	10	10	10
-CARDIOMYOPATHY		3	6	3
-M- ATRIO CAVAL EPITHELIAL MESOTHELIOMA		0	0	0
AORTA	NUMBER EXAMINED:	9	10	10
LUNGS	NUMBER EXAMINED:	10	10	10
-HYPERPLASTIC NODULE		0	0	0
-PLEURITIS WITH SUBADJACENT CHRONIC PNEUMONIA		0	0	0
-PULMONARY EDEMA		0	0	0
-VASCULAR CONGESTION		0	0	0
-THROMBUS		0	0	0
THYMUS	NUMBER EXAMINED:	6	7	9
-PLEURITIS		0	0	0
SPLEEN	NUMBER EXAMINED:	10	10	10
-LYMPHOID HYPERPLASIA OF THE SPLENIC CORPUSCLES		0	0	0
-FIBROSIS CAPSULAR		1	0	1
-INFARCTION		0	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = INTERIM SACRIFICE 1
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S	ANIMAL S E X: / DOSAGE GROUP: / NO. IN GROUP:	-- A N I M A L S A F F E C T E D -- -- MALES -- CTLS	1	2
LYMPH NODES	NUMBER EXAMINED:	10	9	10
-LYMPHOID HYPERPLASIA		0	0	0
LIVER	NUMBER EXAMINED:	10	10	10
-CAPSULAR FOREIGN GRANULOMATOUS REACTION		0	-10	-10
-BILE DUCTULE EPITHELIAL HYPERPLASIA		9	10	10
-HEPATITIS		3	3	2
-FOCUS BASOPHILIC		1	0	2
-HEPATOCYTIC VACUOLIZATION		1	1	0
-TELANGIECTASIS		0	1	0
-NECROSIS		0	5	1
-FIBROSIS CAPSULAR NO COMPOUND		2	0	0
-FOCUS CLEAR		0	0	0
-M- MONONUCLEAR CELL LEUKEMIA		0	0	0
KIDNEY	NUMBER EXAMINED:	10	10	10
-PROGRESSIVE RENAL DISEASE		10	9	10
URINARY BLADDER	NUMBER EXAMINED:	10	10	10
PROSTATE	NUMBER EXAMINED:	10	10	10
-ACUTE SUPPURATIVE PROSTATITIS		0	3	1
-CHRONIC PROSTATITIS		1	0	1
COAG GL	NUMBER EXAMINED:	8	10	10
SEMINAL VESICLE	NUMBER EXAMINED:	10	10	10
EPIDIDYMIS	NUMBER EXAMINED:	10	10	10
TESTES	NUMBER EXAMINED:	10	10	10
-TUBULAR ATROPHY		0	1	0
-INTERSTITIAL CELL HYPERPLASIA		8	0	6
-B-MESOTHELIOMA		0	0	1
DUODENUM	NUMBER EXAMINED:	10	10	10
-COMPOUND-RELATED REACTION WITH ASSOCIATED INFLAMMATION		0	0	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = INTERIM SACRIFICE 1
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S		-- A N I M A L S A F F E C T E D --		
ANIMAL S E X:		-- MALES --		
DOSAGE GROUP:		CTLS	1	2
NO. IN GROUP:		10	10	10
JEJUNUM	NUMBER EXAMINED:	10	8	10
-COMPOUND-RELATED INFLAMMATORY REACTION		0	0	0
-ACUTE PERITONITIS		0	0	0
-TO AUTOLYZED TO TELL ORIGIN		0	0	0
ILEUM	NUMBER EXAMINED:	9	9	10
-COMPOUND-RELATED INFLAMMATORY REACTION		0	0	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0
PANCREAS	NUMBER EXAMINED:	10	10	10
-PERITONITIS		0	1	0
-ACINAR (EXOCRINE) ATROPHY		0	1	2
CECUM	NUMBER EXAMINED:	9	10	9
-COMPOUND-RELATED INFLAMMATORY REACTION		0	1	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0
RECTUM	NUMBER EXAMINED:	9	6	8
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0
COLON	NUMBER EXAMINED:	9	10	10
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0
-COMPOUND PRESENT WITH INFLAMMATORY REACTION		0	0	0
STOMACH	NUMBER EXAMINED:	10	10	10
-VILLUS ATROPHY AND/OR AUTOLYSIS		0	1	0
-COMPOUND-RELATED INFLAMMATORY REACTION		0	0	0
-SEROSAL FIBROSIS		0	1	0
-GLANDULAR CYST(S)		0	0	1
-SEVERE AUTOLYSIS		0	0	0
SKELETAL MUSCLE	NUMBER EXAMINED:	9	10	10
-ACUTE MYOSITIS		0	0	0
SCIATIC NERVE	NUMBER EXAMINED:	7	9	10

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = INTERIM SACRIFICE 1
CTLS = CONTROLS FROM GROUP(S): 3

TISSUES WITH FINDINGS	ANIMAL SEX:	-- ANIMALS AFFECTED -- MALES -- CTLS	1	2
	DOSAGE GROUP:			
	NO. IN GROUP:	10	10	10
TONGUE	NUMBER EXAMINED:	10	10	10
SKIN	NUMBER EXAMINED:	10	10	10
-COMPOUND PRESENT WITH ASSOCIATED INFLAMMATION\FIBROSIS		0	1	0
-INFLAMMATORY EXUDATE ON SKIN SURFACE		0	0	0
-PROCEDURE RELATED GRANULOMATOUS CELLULITIS SUBCUTIS		0	0	0
-NON-SUPPURATIVE DERMATITIS		0	0	0
MAMMARY GLANDS	NUMBER EXAMINED:	6	8	5
-HYPERPLASIA AND/OR HYPERTROPHY OF THE ACINAR TISSUE		0	0	0
NOSE/TURBINATES	NUMBER EXAMINED:	10	10	10
-ACUTE INFLAMMATION		0	1	0
BONE, STERNUM	NUMBER EXAMINED:	10	10	10
BONE, FEMUR	NUMBER EXAMINED:	9	10	10
-HYPERPLASIA MYELOID		0	0	0
BONE VERT	NUMBER EXAMINED:	10	10	10
SPINAL CORD	NUMBER EXAMINED:	10	10	10
ADRENAL	NUMBER EXAMINED:	10	10	10
-B- CORTICAL ADENOMA		0	0	1
PITUITARY GLAND	NUMBER EXAMINED:	9	10	10
-B- ADENOMA		1	0	1
-CYST(S)		0	0	0
-HEMORRHAGE		0	0	0
EYES & OPTIC N.	NUMBER EXAMINED:	10	10	10
-METAPLASTIC BONE SCLERAL		0	0	0
-CORNEAL MINERALIZATION		1	0	0
-PROGRESSIVE RETINAL ATROPHY		0	0	2
-SCLERAL MINERALIZATION		0	0	1
-CORNEAL PIGMENTATION		0	0	0
-CORNEAL VASCULARIZATION		0	0	0
-CHRONIC KERATITIS		0	0	0
-IRIDOCYCLITIS		0	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = INTERIM SACRIFICE 1
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S		-- A N I M A L S A F F E C T E D -- ANIMAL S E X: -- MALES -- DOSAGE GROUP: CTLS	1	2
	NO. IN GROUP:	10	10	10
EAR	NUMBER EXAMINED:	10	10	10
AUDITORY SEBACEOUS	NUMBER EXAMINED:	8	9	7
ABDOMINAL WALL	NUMBER EXAMINED:	0	0	0
-INFECTION AND INFLAMMATION SEVERE INVOLVING THE MUSCULATURE AND PERITONEAL SURFACE		0	0	0
THORAX	NUMBER EXAMINED:	0	0	0
-M-MALIGNANT UNDEFINED SPINDLE CELL SARCOMA PROBABLY NEUROFIBRO SARCOMA		0	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

LETTERMAN ARMY INSTITUTE OF RESEARCH
DIV OF RES SUPP, PATH SERV GP
PRESIDIO OF SAN FRANCISCO, CA 94129
SPECIES: RAT/FISCHER-344

INCIDENCE SUMMARY OF MICROSCOPIC OBSERVATIONS(ALL FINDING)
STUDY NUMBER: GLP83009
PATHOLOGIST(S): MELLICK, PAUL W., Smith, Catherine D
STUDY START DATE: 23-JAN-84

PRINTED: 30-JAN-86
PAGE: 1
STUDY TYPE: CHRONIC/2 YR CARCINOGENIC

NOTES: ANIMALS = INTERIM SACRIFICE 2
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S	ANIMAL S E X:	-- A N I M A L S A F F E C T E D -- -- FEMALES --		
	DOSAGE GROUP:	CTLS	1	2
	NO. IN GROUP:	10	10	10
BRAIN	NUMBER EXAMINED:	10	10	10
TRACHEA	NUMBER EXAMINED:	10	10	10
THYROID GLANDS	NUMBER EXAMINED:	10	10	10
PARATHYROID	NUMBER EXAMINED:	9	7	7
ESOPHAGUS	NUMBER EXAMINED:	9	7	9
SALIVARY GLAND	NUMBER EXAMINED:	10	10	9
LACRIMAL GLAND	NUMBER EXAMINED:	10	10	10
EXORBITAL LACRIM	NUMBER EXAMINED:	8	8	9
HEART	NUMBER EXAMINED:	10	10	10
-CARDIOMYOPATHY		2	2	2
-M- ATRIO CAVAL EPITHELIAL MESOTHELIOMA		0	0	0
AORTA	NUMBER EXAMINED:	9	8	10
LUNGS	NUMBER EXAMINED:	10	10	10
-HYPERPLASTIC NODULE		0	1	0
-PLEURITIS WITH SUBADJACENT CHRONIC PNEUMONIA		0	0	1
-PULMONARY EDEMA		0	0	0
-VASCULAR CONGESTION		0	0	0
-THROMBUS		0	0	0
THYMUS	NUMBER EXAMINED:	5	9	10
-PLEURITIS		0	0	1
SPLEEN	NUMBER EXAMINED:	10	10	10
-LYMPHOID HYPERPLASIA OF THE SPLENIC CORPUSCLES		0	1	0
-FIBROSIS CAPSULAR		0	0	0
-INFARCTION		0	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = INTERIM SACRIFICE 2
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S	ANIMAL S E X: / DOSAGE GROUP: / NO. IN GROUP:	-- A N I M A L S A F F E C T E D -- -- FEMALES -- CTLS	1	2
LYMPH NODES	NUMBER EXAMINED:	10	10	10
-LYMPHOID HYPERPLASIA		0	1	0
LIVER	NUMBER EXAMINED:	10	10	10
-CAPSULAR FOREIGN GRANULOMATOUS REACTION		0	-10	-9
-BILE DUCTULE EPITHELIAL HYPERPLASIA		7	9	8
-HEPATITIS		3	6	3
-FOCUS BASOPHILIC		2	3	1
-HEPATOCYTIC VACUOLIZATION		0	2	1
-TELANGIECTASIS		0	0	0
-NECROSIS		0	0	0
-FIBROSIS CAPSULAR NO COMPOUND		1	0	0
-FOCUS CLEAR		1	0	0
-M- MONONUCLEAR CELL LEUKEMIA		0	0	0
KIDNEY	NUMBER EXAMINED:	10	10	10
-PROGRESSIVE RENAL DISEASE		3	5	2
URINARY BLADDER	NUMBER EXAMINED:	7	9	7
UTERUS	NUMBER EXAMINED:	10	10	10
-COMPOUND PRESENT WITH REACTION		0	0	0
-DILATATION OF THE UTERINE LUMEN (HYDROMETRA)		3	0	0
-PYOMETRA		1	0	0
-ENDOMETRIAL STROMAL POLYP		0	0	1
OVARIES	NUMBER EXAMINED:	10	10	10
DUODENUM	NUMBER EXAMINED:	10	10	10
-COMPOUND-RELATED REACTION WITH ASSOCIATED INFLAMMATION		0	0	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0
JEJUNUM	NUMBER EXAMINED:	10	6	10
-COMPOUND-RELATED INFLAMMATORY REACTION		0	1	0
-ACUTE PERITONITIS		0	0	0
-TO AUTOLYZED TO TELL ORIGIN		0	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = INTERIM SACRIFICE 2
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S	ANIMAL S E X: / DOSAGE GROUP: / NO. IN GROUP:	-- A N I M A L S A F F E C T E D -- -- FEMALES -- CTLS	1	2
ILEUM	NUMBER EXAMINED:	9	9	10
-COMPOUND-RELATED INFLAMMATORY REACTION		0	0	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0
PANCREAS	NUMBER EXAMINED:	10	10	9
-PERITONITIS		0	1	0
-ACINAR (EXOCRINE) ATROPHY		0	0	0
CECUM	NUMBER EXAMINED:	10	10	10
-COMPOUND-RELATED INFLAMMATORY REACTION		0	0	0
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0
RECTUM	NUMBER EXAMINED:	8	7	8
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0
COLON	NUMBER EXAMINED:	9	10	10
-TOO AUTOLYZED TO TELL ORIGIN		0	0	0
-COMPOUND PRESENT WITH INFLAMMATORY REACTION		0	0	0
STOMACH	NUMBER EXAMINED:	9	10	10
-VILLUS ATROPHY AND/OR AUTOLYSIS		0	0	0
-COMPOUND-RELATED INFLAMMATORY REACTION		0	2	0
-SEROSAL FIBROSIS		0	0	0
-GLANDULAR CYST(S)		0	0	0
-SEVERE AUTOLYSIS		0	0	0
SKELETAL MUSCLE	NUMBER EXAMINED:	9	10	10
-ACUTE MYOSITIS		0	0	0
SCIATIC NERVE	NUMBER EXAMINED:	7	9	10
TONGUE	NUMBER EXAMINED:	10	10	10
SKIN	NUMBER EXAMINED:	10	9	9
-COMPOUND PRESENT WITH ASSOCIATED INFLAMMATION\FIBROSIS		0	0	0
-INFLAMMATORY EXUDATE ON SKIN SURFACE		0	0	0
-PROCEDURE RELATED GRANULOMATOUS CELLULITIS SUBCUTIS		0	0	0
-NON-SUPPURATIVE DERMATITIS		0	0	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = INTERIM SACRIFICE 2
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S	ANIMAL S E X: / DOSAGE GROUP: / NO. IN GROUP:	-- A N I M A L S A F F E C T E D -- -- FEMALES -- CTLS	1	2
MAMMARY GLANDS	NUMBER EXAMINED:	9	4	6
-HYPERPLASIA AND/OR HYPERTROPHY OF THE ACINAR TISSUE		0	0	0
NOSE/TURBINATES	NUMBER EXAMINED:	10	10	10
-ACUTE INFLAMMATION		0	0	1
BONE, STERNUM	NUMBER EXAMINED:	10	10	10
BONE, FEMUR	NUMBER EXAMINED:	10	10	9
-HYPERPLASIA MYELOID		0	0	0
BONE VERT	NUMBER EXAMINED:	10	10	10
SPINAL CORD	NUMBER EXAMINED:	10	10	10
ADRENAL	NUMBER EXAMINED:	10	10	10
-B- CORTICAL ADENOMA		0	0	0
PITUITARY GLAND	NUMBER EXAMINED:	10	10	10
-B- ADENOMA		0	0	0
-CYST(S)		3	0	2
-HEMORRHAGE		0	0	0
EYES & OPTIC N.	NUMBER EXAMINED:	10	10	10
-METAPLASTIC BONE SCLERAL		0	1	0
-CORNEAL MINERALIZATION		2	3	2
-PROGRESSIVE RETINAL ATROPHY		0	0	0
-SCLERAL MINERALIZATION		0	0	0
-CORNEAL PIGMENTATION		0	0	1
-CORNEAL VASCULARIZATION		1	0	0
-CHRONIC KERATITIS		2	0	0
-IRIDOCYCLITIS		0	0	0
EAR	NUMBER EXAMINED:	10	10	10
AUDITORY SEBACEOUS	NUMBER EXAMINED:	9	10	9

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CO = 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

NOTES: ANIMALS = INTERIM SACRIFICE 2
CTLS = CONTROLS FROM GROUP(S): 3

T I S S U E S W I T H F I N D I N G S		-- A N I M A L S A F F E C T E D --		
ANIMAL S E X:		-- FEMALES --		
DOSAGE GROUP:		CTLS	1	2
NO. IN GROUP:		10	10	10
ABDOMINAL WALL	NUMBER EXAMINED:	0	0	0
-INFECTION AND INFLAMMATION SEVERE INVOLVING THE MUSCULATURE AND PERITONEAL SURFACE		0	0	0
THORAX	NUMBER EXAMINED:	0	1	0

NOTE: ENTRIES FLAGGED WITH A - (MINUS) ARE SIGNIFICANTLY DIFFERENT FROM CONTROL AT THE 0.05 LEVEL USING KOLMOGOROV-SMIRNOV TWO-TAILED TEST.

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